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Ann. rheum. Dis. (1961), **20**, 215.

HEREDITARY FACTORS IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

BY

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WITH A STATISTICAL APPENDIX BY

T. J. D. ERLEE AND E. F. DRION

There have been few scientifically acceptable publications on the significance of hereditary factors in various rheumatic diseases. Only in the past few years has attention been given to reliable differential diagnosis between the various forms of rheumatism. Of the older authors we may mention Fox and van Breemen (1934), who spoke of the "red thread of secondary cases" of various rheumatic affections which might be observed in the family of a rheumatic patient. Hangarter (1938), who presented a survey of the literature on the subject, believed that various rheumatic conditions, such as rheumatic fever, rheumatoid arthritis, ankylosing spondylitis, and osteo-arthritis, might occur side by side in certain families. These authors attached considerable importance to the so-called "rheumatic diathesis". Holsti and Huuskonen (1938) reported a mass examination (by inquiry) among 195,000 Finnish subjects; 0·9 per cent. were found to be suffering from some rheumatic condition, and various forms of rheumatism occurred in the same family.

Of the current investigators in this field, Stecher and his co-workers should be mentioned first. Stecher (1957), who reported exhaustive personal observations with a comprehensive survey of the literature, maintained that any study of heredity should be based on patients in whom the diagnosis had been made with meticulous accuracy, and that the data considered should be only those pertaining to the diseases chosen as a starting point. He believed that a specific hereditary mechanism was involved in every form of articular rheumatism, not excluding the various forms of arthrosis and spondylosis deformans. It should be borne in mind that a possible "hereditary factor" does not *per se* determine the manifestation of a rheumatic condition, and that other endogenous and exogenous factors also govern the actual appearance of the rheumatic affection.

The familial occurrence and possible involvement of a hereditary factor in ankylosing spondylitis (Bechterew's disease) had previously attracted our attention, and it was decided to institute an investigation of possible hereditary factors and to include rheumatoid arthritis in our survey.

Method and Material

Probands.—From the patients of the "Groningen Rheumatic Centre" we obtained a random series of 100 cases of ankylosing spondylitis and 100 cases of rheumatoid arthritis. A control group of 100 subjects normal at that time was also included. These 300 probands were aged between 25 and 45, and an attempt was made to avoid predominance of either sex.

Diagnosis.—The diagnosis of rheumatoid arthritis had to be "definitive" (Ropes, Bennett, Cobb, Jacox, and Jessar, 1957).

Ankylosing spondylitis was regarded as "definitive" in patients showing typical *x*-ray changes in the sacro-iliac joints and sometimes the vertebral column, spinal ankylosis, and a typical history and symptoms.

The probands of the control group were also examined (at the out-patient clinic), and only those were included who were quite free from arthritis and spondylitis.

In determining the results of the subsequent examination of the relatives of these 300 probands, the same criteria were used as regards a possible diagnosis of "rheumatoid arthritis" or "ankylosing spondylitis".

Relatives.—The completest possible pedigree was obtained for each of the 300 probands. All accessible grandparents, parents, siblings, children, and collateral members of the family were examined.

Persons under 15 years of age were omitted from the investigation for two reasons:

(*i*) Rheumatoid arthritis and ankylosing spondylitis are exceedingly rare before the 15th year.

(*ii*) Comparison was thereby facilitated between our results and those of other mass investigations in the Netherlands, which were also limited to subjects aged 15 years and over (de Blécourt, 1951a, b, 1954; de Graaff, 1961).

All the relatives were examined at home by the same specially trained physician. If the diagnosis was doubtful the subject was referred to a rheumatic diseases out-patient clinic for further investigation.

Results

Completion Rate.—A rate of 100 per cent. is obviously impossible to obtain in an investigation covering some thousands of relatives. The co-operation offered by all agencies and persons concerned proved to be such, however, that a rate of nearly 87 per cent. was achieved. The details are shown in Table I, which should be read as follows:

Rheumatoid Arthritis.—The average age of the 100 probands of this group (38 males and 62 females) was 38·8 years: the total number of their relatives was 3,256, but only 2,842 of these were over 15 years of age. Of this number 2,486 (87·5 per cent.) were contacted and included in the survey.

Ankylosing Spondylitis.—The average age of the 100 probands of this group (76 males and 24 females) was 36·7 years: their relatives numbered 3,170, of whom 2,862 were over 15 years of age; 2,478 (86·6 per cent.) were included.

Healthy Controls.—The average age of the 100 probands of this group (48 males and 52 females) was 38·6 years: their relatives numbered 3,141, of whom 2,825 were over 15; 2,441 (86·4 per cent.) were included.

Total.—The three groups together included 8,529 relatives aged 15 years and over, of whom 7,405 (86·8 per cent.) were included in the investigation.

Secondary Cases.—The occurrence of secondary cases in the three groups of relatives is shown in Table II (opposite):

Rheumatoid Arthritis Group.—Among 2,486 relatives, there were 58 cases (2·35 per cent.). The occurrence of such secondary cases was higher amongst female relatives (3·48 per cent.) than amongst male relatives (1·25 per cent.).

These percentages may be contrasted with the occurrence of only twenty secondary cases of rheumatoid arthritis amongst the 2,441 relatives of the control group (0·82 per cent.): amongst male relatives 0·4 per cent. and amongst female relatives, 1·2 per cent.

Ankylosing Spondylitis Group.—Among 2,478 relatives, 45 secondary cases of ankylosing spondylitis were found (1·8 per cent.). But here, in contrast to the experience in the rheumatoid arthritis group, the occurrence of secondary cases was higher amongst the male relatives (2·45 per cent.) than amongst the female relatives (1·20 per cent.).

Control Group.—There were only two "secondary" cases of ankylosing spondylitis amongst the 2,441 relatives of the controls (0·08 per cent.): amongst males 0·17 per cent. but amongst females nil.

Affected Families.—Table III (opposite) shows for each group the porportion of families with 0, 1, 2, etc., secondary cases of the same disease.

Rheumatoid Arthritis Group.—There were 34 families showing 58 secondary cases, *i.e.* a familial occurrence of 34 per cent. Of these 34 familial occurrences, fifteen were *via* the male and thirteen

TABLE I

PERSONS INCLUDED IN THE SURVEY

Group	Rheumatoid Arthritis (100 probands: 38 M., 62 F.)			Ankylosing Spondylitis (100 probands: 76 M., 24 F.)			Healthy Controls (100 probands: 48 M., 52 F.)			All Groups
	M.	F.	Total	M.	F.	Total	M.	F.	Total	Total
Total Relatives	1,677	1,579	3,256	1,585	1,585	3,170	1,574	1,567	3,141	9,567
Deduct those under 15 yrs of age	211	203	414	162	146	308	166	150	316	1,038
Suitable for Inclusion	1,466	1,376	2,842	1,423	1,439	2,862	1,408	1,417	2,825	8,529
Inaccessible	188	168	356	196	188	384	203	181	384	1,124
Number Included	1,278	1,208	2,486	1,227	1,251	2,478	1,205	1,236	2,441	7,405
Percentage of No. Suitable for Inclusion	87·2	87·8	87·5	86·2	86·9	86·6	85·6	87·2	86·4	86·8

TABLE II

PREVALENCE OF SECONDARY CASES AMONGST RELATIVES

	Relatives	Rheumatoid Arthritis			Ankylosing Spondylitis			Controls				
		No. of Relatives	With RA		No. of Relatives	With AS		No. of Relatives	With RA		With AS	
			No.	Per cent.		No.	Per cent.		No.	Per cent.	No.	Per cent.
Male	Sons	51	—	—	14	—	—	29	—	—	—	—
	Brothers	228	3	1·3	200	15	7·5	231	1	—	1	—
	Fathers	91	4	4·4	97	5	5·15	92	1	—	—	—
	Uncles	295	2	0·68	296	6	2·03	279	2	—	1	—
	Grandfathers	121	3	2·4	117	1	0·84	111	—	—	—	—
	Male Cousins	492	4	0·81	500	3	0·6	463	1	—	—	—
	Total	1,278	16	1·25	1,224	30	2·45	1,205	5	0·41	2	0·17
Female	Daughters	46	—	—	41	1	0·24	32	—	—	—	—
	Sisters	235	9	3·8	201	9	4·47	237	4	—	—	—
	Mothers	90	9	10·0	94	—	—	97	3	—	—	—
	Aunts	279	11	3·9	314	1	0·31	304	3	—	—	—
	Grandmothers	123	7	5·7	107	—	—	115	1	—	—	—
	Female Cousins	435	6	1·38	497	4	0·81	451	4	—	—	—
	Total	1,208	42	3·48	1,254	15	1·20	1,236	15	1·21	—	—
Total Male and Female Relatives		2,486	58	2·35	2,478	45	1·81	2,441	20	0·82	2	0·08

TABLE III

FAMILIES OF PROBANDS—ACCORDING TO THE NUMBER OF SECONDARY CASES

No. of Secondary Cases	RA Probands	AS Probands	Control Probands	
			with RA in Family	with AS in Family
0	66	70	81	98
1	20	20	18	2
2	7	6	1	—
3	5 (34)	3 (30)	— (19)	— (2)
4	1	1	—	—
5	1	—	—	—
Total	100	100	100	100

via the female line of descent, and six concerned a brother and/or sister.

Ankylosing Spondylitis Group.—There were thirty families with 45 secondary cases, *i.e.* a familial occurrence of 30 per cent. Of these thirty familial occurrences, ten were *via* the male and eight *via* the female line of descent, and twelve concerned a brother and/or sister.

Control Group.—There were nineteen families with twenty "secondary" cases of rheumatoid arthritis: only one family included two cases and these affected an uncle and a female cousin in the same line of descent. There were only two families with secondary cases of ankylosing spondylitis (one in each, and both males).

Families with both Rheumatoid Arthritis and Ankylosing Spondylitis.—The affected relatives in the rheumatoid arthritis group included two cases of ankylosing spondylitis (0·08 per cent.); one of these occurred in a family which also had two secondary rheumatoid arthritis cases (in the same line of descent).

The affected relatives in the ankylosing spondylitis group included fifteen cases of rheumatoid arthritis (0·61 per cent.): five in males and ten in females; eight of these cases occurred in families with one or more cases of secondary ankylosing spondylitis, including six in the same line of descent.

Other Forms of Rheumatism.—Although an investigation into the occurrence of other forms of articular rheumatism such as osteo-arthritis and rheumatic fever was not included in our terms of reference, an attempt was nevertheless made to gain some general impression in this respect. Only in very marked cases were these diagnoses registered. Not too much value should therefore be attached to this part of the investigation, which yielded the following results:

Rheumatoid Arthritis Group.—This included sixteen cases of rheumatic fever (0·62 per cent.) and 58 cases of osteo-arthritis (2·35 per cent.).

Ankylosing Spondylitis Group.—This included sixteen cases of rheumatic fever (0·8 per cent.) and 64 cases of osteo-arthritis (2·6 per cent.).

Control Group.—This included eight cases of rheumatic fever (0·32 per cent.) and 34 cases of osteo-arthritis (1·39 per cent.).

A detailed statistical report on these results is given in the Appendix, from which the following conclusions may be quoted here:

"The data indicate that both rheumatoid arthritis and ankylosing spondylitis are capable of familial occurrence and that, consequently, each probably has a hereditary component; it is also indicated that the hereditary components of the two conditions are different in kind.

It may also be noted that the frequency of rheumatoid arthritis found in the control group agreed with that established in the course of the mass investigation into rheumatoid arthritis made by de Graaff (1961).

It appears that about one-third of the families in the Netherlands are affected by rheumatoid arthritis, and about one in seventeen with ankylosing spondylitis.

Both rheumatoid arthritis and ankylosing spondylitis therefore appear to be characterized by familial occurrence and a hereditary component, but the same familial and/or hereditary component is not involved in both these forms of articular rheumatism."

Discussion

Our results thus give support to the view that rheumatoid arthritis and ankylosing spondylitis are not varieties of the same entity, but in some familial and hereditary studies this difference has not been sufficiently taken into account, so that comparison with our investigation is difficult. Comparison is also impeded by the fact that some investigators do not specify the relationship between the proband and other relatives examined; nor do they mention the completion rate or the composition of the control group. Some of the results obtained by various groups of workers between 1950 and 1959 are summarized in Table IV.

The first striking feature of our results is the predominance of secondary cases among female relatives in the rheumatoid arthritis group (3·48 per cent. as against 1·25 per cent. in males), and the predominance of secondary cases among male relatives in the ankylosing spondylitis group (2·45

TABLE IV

INCIDENCE OF SECONDARY CASES REPORTED BY OTHER AUTHORS

Authors	Date	Disease in Probands	Percentage Secondary Cases	
			Relatives	Controls
Stecher	1957	AS	2·5	0·18
		RA	3·1	0·58
Neri Serneri and Bartoli	1956	RA	6·3	0·38
Miall	1955	RA	3·1	0·6
Barter	1952	RA	11·0	4·6
E.R.C.	1950	RA	Fathers 7·0 Mothers 15·0 Siblings 3·8	3·0 9·0 1·8
Short, Abrams, and Sartwell	1952	RA	11·9	5·1
Whittinghill	1959	RA	3	—
		AS	First degree 6·3 Second degree 2·3 3rd degree 0·7	— — —
Lawrence and Ball	1958	RA	9·0	2·0
Ziff, Schmid, Lewis, and Tanner	1958	RA	3·4	—
Bremner, Alexander, and Duthie	1959	RA	Clinical and subclinical 7·6 Clinical 4·9	—

per cent. as against 1·20 per cent. in females). This is entirely in accordance with the general experience that rheumatoid arthritis occurs more frequently in females and ankylosing spondylitis in males.

These secondary cases were seen *via* both the paternal and maternal lines of descent and gonasomal factors (the X- and Y-chromosomes) are thus unlikely to be of great importance in the hereditary mechanism of these two conditions.

The female and male predominance in rheumatoid arthritis and ankylosing spondylitis respectively might suggest a sex-linked dominance, but we have seen mothers with ankylosing spondylitis who have sons suffering from the same disease, and also fathers with daughters who suffered from rheumatoid arthritis. Stecher (1957) believes that the occurrence of ankylosing spondylitis in a female patient results in an increase in the so-called penetrance (manifestation of an existing hereditary disposition) in the family concerned. Secondary cases were connected with ten of our 24 female probands (41 per cent.) and twenty of our 76 male probands (26 per cent.), and on the basis of these figures our statistician did not wish to go beyond the opinion that there is possibly a "tendency towards promotion of penetrance" in the family of a female proband with ankylosing spondylitis.

The finding of 0·82 per cent. rheumatoid arthritis and 0·08 per cent. ankylosing spondylitis in our control group of 2,441 subjects is in good agreement with the result of a (limited) mass investigation into the frequency of rheumatic conditions carried out in the Groningen area during 1950-1952. Among 3,378 subjects (all over age 15), 1 per cent. had rheumatoid arthritis and 0·1 per cent. had ankylosing spondylitis.

The results of the mass investigation more recently carried out in the Netherlands (to be published, de Graaff, 1961) also agree with the above data, which suggests that about 1 per cent. of the Dutch population suffer from rheumatoid arthritis (unmistakable, though sometimes asymptomatic), while about 0·1 per cent. suffer from ankylosing spondylitis.

Secondary cases were found in nearly three times as many of the relatives of subjects in the rheumatoid arthritis group as in the control group, and in over 22 times as many of the relatives of the ankylosing spondylitis group as in the control group. This indicates that the hereditary component is more important in ankylosing spondylitis than in rheumatoid arthritis. The higher degree of morbidity in first-degree relatives (especially in the case of ankylosing spondylitis) indicates a dominant hereditary mechanism (see Table II). A recessive hereditary mechanism should, however, be indicated by an increased frequency of consanguineous marriages in the rheumatoid arthritis and in the ankylosing spondylitis group. But consanguineous marriages (determined from civil registration documents up to and including the great-grandparents) were encountered in only one case in the rheumatoid arthritis group, not at all in the ankylosing spondylitis group, and in one case in the control group.

In the two cases of consanguinity, no influence on the occurrence of rheumatoid arthritis (or ankylosing spondylitis) was demonstrable. The consanguineous family in the control group included no case of "rheumatism"; that in the rheumatoid arthritis group included three cases of rheumatoid arthritis in the maternal line (the father's grandparents were first-degree cousins).

It should be pointed out that none of the probands with rheumatoid arthritis or ankylosing spondylitis had parents who were *both* suffering from the same disease as the proband. This eliminates the occurrence of homozygotes.

Our investigation suggests that both rheumatoid arthritis and ankylosing spondylitis probably involve a non-sex-linked dominant hereditary mechanism, with differences in penetrance between males and females. This accords with the view held by Stecher (1957).

Several investigators, including Short and others (1952) believed that they had observed an increased number of cases of "rheumatism" (all forms) among the relatives of subjects with rheumatoid arthritis and ankylosing spondylitis. We also noticed a trend in this direction, as there were more cases of osteo-arthritis and rheumatic fever in the relations of patients with rheumatoid arthritis and ankylosing spondylitis than in the control group. The statistician was reluctant to base a conclusion on this observation, however, because the differences were relatively slight, and because our investigation was not especially aimed at these conditions.

Although a serological examination (Rose test) was frequently included in the examination of probands and relatives, the figures are insufficient for an investigation into the possible correlation between a positive Rose test and hereditary factors in rheumatoid arthritis which has been suggested by Ziff and others (1958), Lawrence and Ball (1958), and Bremner and others (1959). We have now started an investigation into the correlation between the so-called rheumatoid arthritis factor and the occurrence of secondary cases. Moesmann (1959) has recently thrown doubt on the existence of a hereditary factor; a study of the occurrence of rheuma-

toid arthritis in heterozygotic and homozygotic twins does not appear to support the view that heredity is important. Our personal observations, however, lead us to maintain that both rheumatoid arthritis and ankylosing spondylitis are likely to involve a non-sex-linked dominant hereditary mechanism, with differences in penetrance between males and females.

Summary

7,405 relatives (down to and including third-degree kin) of 300 probands (100 with rheumatoid arthritis, 100 with ankylosing spondylitis, and 100 normal controls) were examined for rheumatoid arthritis or ankylosing spondylitis.

The frequency of rheumatoid arthritis among relatives of the rheumatoid arthritis group was 2·8 times as high as that in the control group; the frequency of ankylosing spondylitis among relatives of the spondylitis group was 22·6 times as high as that in the control group. Ankylosing spondylitis was as frequent in the rheumatoid arthritis group as in the control group. The same holds true for rheumatoid arthritis relative to ankylosing spondylitis. Both rheumatoid arthritis and ankylosing spondylitis, therefore, probably involve a non-sex-linked dominant hereditary mechanism with differences in penetrance between males and females.

One-third of all Dutch families are thus believed to be affected by rheumatoid arthritis.

This investigation was carried out with the financial and statistical help of the Health Organization T.N.O., The Hague.

REFERENCES

Barter, R. A. (1952). *Ann. rheum. Dis.*, **11**, 39.
Blécourt, J. J. de (1951a). *Rev. Rhum.*, **18**, 639.
—— (1951b). *Ned. T. Geneesk.*, **95**, 3, 763.
—— (1954). *Ann. rheum. Dis.*, **13**, 338.
Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R. (1959). *Ibid.*, **18**, 279.
Empire Rheumatism Council (1950). *Ibid.*, Suppl. vol. 9.
Fox, R. F., and Breemen, J. van (1934). "Chronic Rheumatism." Churchill, London.
Graaff, R. de (1961). Thesis, Leyden. (In the press.)
Hangarter, W. (1938). "Der Rheumatismus", No. 13. Steinkopff, Dresden.
Holsti, Ö., and Huuskonen, A. J. (1938). *Acta med. scand.*, Suppl. 89, p. 128.
Lawrence, J. S., and Ball, J. (1958). *Ann. rheum. Dis.*, **17**, 160.
McKusick, V. (1959). *Amer. J. Med.*, **26**, 283.
Miall, W. E. (1955). *Ann. rheum. Dis.*, **14**, 150.
Moesmann, G. (1959). *Acta rheum. scand.*, **5**, 291.
Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1957). *Ann. rheum. Dis.*, **16**, 118.
Neri Serneri, G. G., and Bartoli, V. (1956). *Acta Genet. med.* (*Roma*), **5**, 402.
Short, C. L., Abrams, N. R., and Sartwell, P. E. (1952). "Rheumatic Diseases: based on the Proceedings of the VII International Congress on Rheumatic Diseases", p. 47. Saunders, Philadelphia.
Stecher, R. M. (1957). "Heredity in Joint Diseases." *Doc. rheum. Geigy*, No. 12. Basel.
Whittinghill, M. (1959). "Proceedings of the 10th International Congress on Genetics, Montreal, 1958", vol. 2, p. 314.
Ziff, M., Schmid, F. R., Lewis, A. J., and Tanner, M. (1958). *Arthr. and Rheum.*, **1**, 392.

STATISTICAL APPENDIX

BY

T. J. D. ERLEE AND E. F. DRION

The relatives over 15 years of age included some 10 per cent. on whom insufficient data were obtained. Table A (opposite) summarizes the unexamined subjects aged 15 and over and those under 15 years of age. In each group, the number of boys under 15 exceeded the number of girls under 15, although the difference is not significant. In the older age groups, too, there were more males than females in each group (difference not significant).

Since it is known that both rheumatoid arthritis and ankylosing spondylitis can become clinically manifest at a fairly advanced age, a complete statistical analysis should take into account the age of all subjects included in the investigation. Since the object of this investigation was more limited (to determine whether there are unmistakable indications of a familial occurrence of the diseases in question), it seems justifiable to omit any consideration of the age distribution. The relatives of probands with rheumatoid arthritis tended to be slightly older than those in the other group; this was seen in the average number of sons and daughters and male and female cousins per family. The older the proband, the greater will be the average number of his descendants. However, the average number of male and female cousins was only slightly larger than the average in the control group (Table B), and since there

TABLE A

INACCESSIBLE RELATIONS

Age (yrs)		Younger than 15 yrs old		Remainder	
Sex		Male	Female	Male	Female
Group	Rheumatoid Arthritis	211	203	188	168
	Ankylosing Spondylitis	162	146	196	188
	Control	166	150	203	181

TABLE B

AVERAGE CHILDREN AND COUSINS PER FAMILY

Group	No. of Children	No. of Male and Female Cousins
Rheumatoid Arthritis	0·97	9·27
Ankylosing Spondylitis	0·58	9·89
Control	0·61	9·14

is no indication that the uncles and aunts were older, elaboration without correction for age distribution would seem to be justified.

Each family in the rheumatoid arthritis group* includes at least one case of rheumatoid arthritis (*viz.* the proband); *mutatis mutandis*, the same holds true for the ankylosing spondylitis group.* The proband of the control group,* however, has neither RA nor AS. It is consequently impossible to make a simple comparison between the total frequency of RA in the RA Group (and of AS in the AS Group) with the frequency of RA and AS, respectively, in the C Group. However, in each group there are subgroups for which this objection does not hold. As probands for each of the three groups, subjects between 25 and 45 years of age were chosen; if the proband is male, then he is likely to be in the same age and sex group as his brothers and male cousins; if the proband is female, then she will belong to the same age and sex group as her sisters and female cousins. Both these groups will be henceforth referred to as the A Category. Subjects of another generation (grandparents, parents, uncles and aunts, sons and daughters) will largely fall outside the age group of the proband; these subjects of another generation than that of the proband, and *all* subjects of the opposite sex, will be referred to as B Category. It is therefore statistically justifiable to make a simple comparison in the B Category between the test and control groups as to the frequency of the diseases under investigation. This comparison is shown in Tables C and D.

* For the sake of simplicity, the three groups will be indicated hereafter as RA Group, AS Group, and C Group, and the diseases as RA and AS.

TABLE C

FAMILIES WITH RHEUMATOID ARTHRITIS

Proband	Number of Families Classified by Number of Cases of RA in B Category					Number of Families with One Case of AS in the Family (A + B Category)
	0	1	2	3	4	
Rheumatoid Arthritis	74	16	6	3	1	2
Control	84	16	0	0	0	2

TABLE D

FAMILIES WITH ANKYLOSING SPONDYLITIS

Proband	Number of Families Classified by Number of Cases of AS in B Category					Number of Families with One or Several Cases of RA in the Family (A + B Category)
	0	1	2	3	4	
Ankylosing Spondylitis	78	17	4	0	1	15+
Control	99	1	0	0	0	19++

\+ All with one patient with RA.
++ Eighteen with one RA patient and one with two RA patients.

It follows from Table C that the B Category of the RA Group has a significantly higher frequency of families with RA than the B Category of the C Group ($P = 0{\cdot}0013$); a similar conclusion is even more firmly true for the AS Group ($P < 0{\cdot}0001$). An analysis of this kind can hardly be carried out for the A Category.

Without further calculation it is obvious that the frequencies of AS in the RA and C Groups are as high as the frequencies of RA in the AS and C Groups.

Thus both RA and AS are characterized by familial occurrence, and while families with RA show no increased occurrence of AS, families with AS do show an increased occurrence of RA. Since this conclusion is based on a study of the B Category, most of the members of which (uncles, aunts, grandparents) do not live in the same house as the proband, this familial occurrence must be explained by the existence of a hereditary component for each condition separately.

The series is sufficiently comprehensive to venture an estimate of the chance of clinical manifestation of each disease both among members of the affected families and among members of the C Group. The value of this estimate of the frequencies of the two diseases investigated is that it affords an impression of the order of magnitude of the phenomenon. A "family" as defined here broadly consists of two groups of non-consanguineous subjects, *viz.* the paternal relatives and the maternal relatives; thus, if one or both diseases is hereditary, the trait will usually prevail in only one of the two branches, and the estimated probability is on the low side.

Former investigations have revealed that clinical symptomatic RA is found in a higher percentage of females than of males, while the reverse is true for AS; the above-mentioned probability therefore, must be calculated for each sex separately. In the RA and the AS Groups, moreover, the probability for male relatives of a male proband and for female relatives of a female proband, must be calculated separately for the A and B Categories. This is because the A Category must always include at least one sick person (*i.e.* the proband). The manner of calculation and the separate results for the A and the B Category will be discussed later. The average probabilities are presented in Table E.

A comparison of the frequencies of RA in the RA and C Groups can be used as a basis for a rough estimate of the proportion of families in the Netherlands which are affected by RA. For each sex the result obtained is about one in three. A corresponding calculation for AS can be made only for males, because this disease did not occur in any female in either the C or the RA Group. The result for males suggests that ankylosing spondylitis occurs in only one out of seventeen Dutch families.

Calculations

The probability of occurrence of one of the two conditions equals the average frequency of the disease, making the necessary correction (in the A Category) for the fact that at least one patient (the proband) has the disease.

(1) The probabilities in the C Group were calculated by dividing the number of affected subjects of each sex by the total number of subjects of that sex.

(2) The probability of RA in the AS Group and of AS in the RA Group were calculated for each sex separately in the manner indicated under (1).

(3) The probability of RA in the B Category in the RA Group and of AS in the AS Group was calculated for each sex as indicated under (1).

(4) In calculating the probability of RA and AS, respectively, in the A Category, the fact that at least one patient (the proband) is present in each family can be allowed for in the following way:

Let p be the probability for the sex under investigation in affected families. Consider all families affected with k subjects in the A Category. The probability that such a family is included in the investigation is $(1-(1-p)^k)$, *viz.* the chance that at least one patient is included in the A Category of this family inducts at least one patient. The mathematical expectation of the number of patients in a family of k subjects is kp. Therefore, the conditional mathematical expectation of the number of patients, provided that at least the proband is present (so that the family is included in the investigation), is

$$\frac{kp}{1-(1-p)^k}.$$

Let the number of patients in the i-th family with k

TABLE E

AVERAGE PROBABILITIES

Group	Average Probability of:			
	Rheumatoid Arthritis		Ankylosing Spondylitis	
	Male	Female	Male	Female
Rheumatoid Arthritis ..	0·013	0·035	0·0008	(0)
Ankylosing Spondylitis ..	0·004	0·008	0·024	0·012
Control	0·004	0·012	0·002	(0)

subjects be a_{ik}, then equating the number found and the expectation gives:

$$a_{ik} = z \frac{kp}{1-(1-p)^k}$$

$$= \frac{kp}{1-(1-\frac{kp}{1!}+\frac{k(k-1)p^2}{2!}-\frac{k(k-1)(k-2)p^3+\ldots.)}{3!}}$$

$$= \frac{kp}{kp-\frac{1}{2}k(k-1)p^2+\frac{1}{6}k(k-1)(k-2)p^3-\ldots.}$$

or

$$\frac{1}{a_{ik}} = 1-\tfrac{1}{2}(k-1)p+\tfrac{1}{6}(k-1)(k-2)p^2-\ldots.$$

Since the maximal value of p found in this investigation was 0·03 (RA Group females), and since the maximal value of k in women of the RA Group is 23, so that in this least favourable case the value of the maximal term omitted is only 0·010, there is no objection to breaking off the series after the term with p^2.

An estimate of p for the whole series is thus obtained by the equation:

$$\frac{\epsilon}{k}\frac{\epsilon}{i}\frac{1}{a_{ik}} = \frac{\epsilon}{k} nk\,(1-\tfrac{1}{2}(k-1)p+\tfrac{1}{6}(k-1)\,(k-2)p^2),$$

in which n^k is the number of families with k subjects in the A Category.

Table F presents the estimates of p obtained by the four methods described above.

TABLE F

ESTIMATES OF PROBABILITY

Group	Category	Rheumatoid Arthritis		Ankylosing Spondylitis	
		Male	Female	Male	Female
Rheumatoid Arthritis	A	0·016	0·030	—	—
	B	0·014	0·047	—	—
	Entire Group	—	—	0·0008	(0)
Ankylosing Spondylitis	A	—	—	0·021	0·026
	B	—	—	0·017	0·008
	Entire Group	0·004	0·008	—	—
Control	Entire Group	0·004	0·012	0·002	(0)

Facteurs héréditaires dans l'arthrite rhumatismale et la spondylarthrite ankylosante

RÉSUMÉ

7.405 parents (jusqu'à et y compris les parents au troisième degré) de 300 sujets (100 cas d'arthrite rhumatismale, 100 cas de spondylarthrite ankylosante et 100 témoins normaux) furent examinés pour rechercher l'arthrite rhumatismale ou la spondylarthrite ankylosante.

La fréquence de l'arthrite rhumatismale parmi les parents du groupe arthritique rhumatismal fut 2,8 fois plus grande que parmi ceux du groupe témoin; la fréquence de la spondylarthrite ankylosante parmi les parents du groupe spondylarthritique fut 22,6 fois plus grande que parmi ceux du groupe témoin. La spondylarthrite ankylosante fut aussi fréquente dans le groupe témoin. Il en fut de même pour l'arthrite rhumatismale en relation à la spondylarthrite ankylosante. Par conséquent, autant l'arthrite rhumatismale que la spondylarthrite ankylosante impliquent probablement un mécanisme héréditaire dominant, sans linkage sexuel, avec des différences de pénétration entre les hommes et les femmes.

On croit qu'un tiers de toutes les familles hollandaises se trouve affecté par l'arthrite rhumatismale.

Factores hereditarios en artritis reumatoide y espondilartritis anquilosante

SUMARIO

7.405 parientes (hasta e incluyendo el parentesco del tercer grado) de 300 sujetos (100 con artritis reumatoide, 100 con espondilartritis anquilosante y 100 personas normales) fueron examinados respecto a artritis reumatoide o espondilartritis anquilosante.

La frecuencia de la artritis reumatoide entre los parientes del grupo con artritis reumatoide fué 2,8 mayor que entre los del grupo testigo; la frecuencia de la espondilartritis anquilosante entre los parientes del grupo con espondilartritis dué 22,6 veces mayor que entre los del grupo testigo. La espondilartritis anquilosante fué tan frecuente en el grupo de artritis reumatoide como en el grupo testigo. Lo mismo fué observado respecto a la artritis reumatoide en relación con la espondilartritis anquilosante. Tanto la artritis reumatoide como la espondilartritis anquilosante implican, pués, probablemente un mecanismo hereditario dominante, sin enlace sexual, con diferencias de penetración entre machos y hembras.

Se cree que una tercera parte de todas las familias holandesas está afectada por artritis reumatoide.

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DIGITAL ARTERITIS IN RHEUMATOID DISEASE*

BY

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Three broad types of vasculitis have been described in rheumatoid arthritis:

(1) Subacute lesions of small vessels found in muscles by Sokoloff, Wilens, and Bunim (1951), and in the heart, muscles, and nerve sheaths by Cruickshank (1954).

(2) Cases of rheumatoid arthritis complicated by severe widespread necrotizing arteritis affecting large vessels and indistinguishable from polyarteritis nodosa (Aronoff, Johnson, and Dworkin, 1960; Ball, 1954; Graef, Hickey, and Altmann, 1949; Levin, Rivo, Scott, Figueroa, Fred, and Barrett, 1953; Nyström, 1953; Ogryzlo, 1953; Schmid, Cooper, Ziff, and McEwen, 1961).

(3) Bywaters (1957) has described patients with digital arterial narrowing due to obliterative endarteritis with evidence of visceral arterial involvement in two autopsied patients. This last type appears morphologically distinct from polyarteritis nodosa, consisting of a bland, sometimes mucoid, intimal proliferation. However, in each of the two autopsied cases described, there were in addition certain arteries with evidence of acute inflammatory disease, past or present, as well as a few arteries with secondary thrombosis and recanalization.

The relation between these three types of lesion is still far from clear.

Virtama (1959) carried out *post-mortem* brachial arteriography in cases of rheumatoid arthritis, and concluded from this that the characteristic alterations were local obliteration and post-stenotic dilation of the digital arteries with arterial dilation near bone erosions.

This paper describes a study of digital lesions in selected patients with rheumatoid arthritis, using the radiological technique of brachial arteriography and correlating this with clinical findings, reactive hyperaemia, and, in some instances, with autopsy or biopsy material.

Methods

To perform brachial arteriography 10 ml. 45 per cent. "Hypaque" are rapidly injected into the brachial artery at the elbow. In the first few patients a general anaesthetic was given and the flow of injected "Hypaque" was controlled by intermittent inflation of a blood-pressure cuff while the films of the hand were obtained (Lynn, Steiner, and Van Wyk, 1955). We now usually give only a local anaesthetic at the site of the injection and dispense with the cuff, taking a rapid series of films at roughly one-second intervals for 8 seconds. No complications have been encountered; there is sometimes mild pain in the hand during the procedure; in one patient there was painful spasm of the brachial and smaller arteries for about 2 minutes.

Reactive hyperaemia (Pickering, 1933) was observed in the warm exsanguinated limb after 4 minutes' ischaemia, delayed flushing in the various digits being timed.

Results

We have performed arteriograms in ten adult patients with rheumatoid arthritis in whom there was some reason to suspect the presence of digital arterial disease. In all ten the arteriogram was abnormal. We have also performed *post-mortem* arteriography and histology in a further case. Because of these abnormal films, arteriography was carried out in two other patients with early rheumatoid arthritis in whom there was no indication of

* Presented at a meeting of the Heberden Society on December 3, 1960.

arteritis, and in both of them the arteriogram was normal. Fig. 1 shows the film of one of these, a woman aged 45 who had had rheumatoid arthritis for one year. The features of this normal arteriogram are the smooth even calibre of the arteries and the presence of two palmar digital vessels in each digit, though the two vessels in any one digit are not always of equal size; in the thumb, index, and little fingers, the median artery is often predominant (Edwards, 1960). The small vessels of the pulps are equally well filled.

Fig. 1.—Normal brachial arteriogram in a patient with early rheumatoid arthritis.

Case Histories

Case 1, a man aged 57, had rheumatoid arthritis which started in 1956, and developed extensive nodule formation. In April, 1957, treatment was commenced with prednisolone 15 mg. daily. In September, 1958, he developed pain in the right leg and was found to have an absent right ankle jerk and impaired cutaneous sensation over the dorsum and outer aspect of the right foot. At the same time small ischaemic lesions first appeared on all the digits of both hands, coming subsequently in recurrent crops (Fig. 2). In April, 1959, the index and middle fingers of the right hand were noticed to be cool, and reactive hyperaemia was delayed in these two fingers

Fig. 2.—Case 1. Digital ischaemic lesions.

(25 and 40 sec.). The differential agglutination titre (D.A.T.) was positive, 1 : 32. Brachial arteriography (Fig. 3) showed many arterial blocks, in both the hand and the fingers. None of the digital vessels was intact except the median artery of the thumb, and this was abnormally tortuous. Of the finger vessels, the most nearly normal was the radial artery of the ring finger, but even here there was interruption and collateral circulation at the level of the middle phalanx.

Fig. 3.—Case 1. Brachial arteriogram.

Case 2, a man aged 50, had rheumatoid arthritis which started in 1952. In 1958, while on salicylate treatment only, he first noticed transient blanching, on exposure to cold, of any of the middle three digits of either hand. In July, 1960, because of progressive arthritis, with nodule formation, treatment with prednisone 10 mg. daily was commenced. The D.A.T. was positive, 1 : 64. In October, the second, third and fourth digits of the left hand became permanently cold and rather blue; thrombotic lesions appeared at the nail-edge. Impaired sensation was now noticed over the dorsum of the left foot. Reactive hyperaemia was slightly delayed in the three involved fingers (3 sec. compared with 1 sec. in the other digits). An arteriogram showed a number of severe abnormalities including a stenosed segment of radial artery and occlusion of all the digital vessels except the ulnar digiti quinti (Fig. 4*a*) and those of the thumb, and only in these two digits was any pulp filling seen.

A biopsy was taken of the occluded radial digital artery of the middle finger (by Mr. S. Harrison). Proximally, at about the middle of the proximal phalanx, the vessel showed thickening of the intima with no inflammation of the intima or adventitia, the lumen being reduced to a slit. Section a few millimetres distal to this point revealed total occlusion with fresh fibrin thrombus and similar intimal thickening around the thrombus. Scanty neutrophil polymorphonuclear leucocytes and histiocytes were present at the periphery of the thrombus and in the adventitia. Further distally again (Fig. 5) there was intimal thickening with organizing thrombus

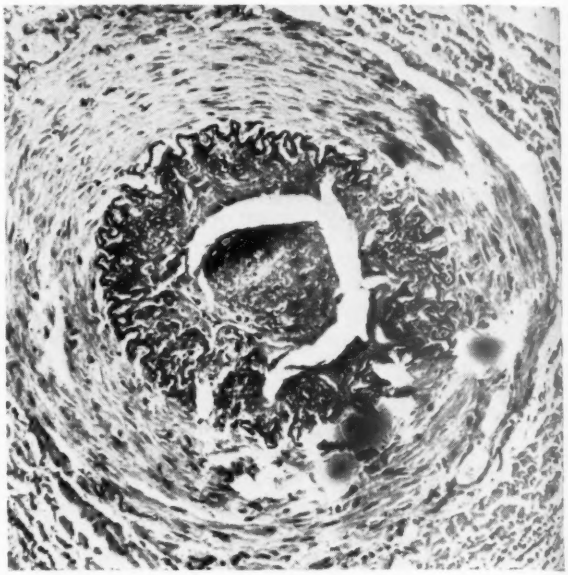

Fig. 5.—Case 2. Digital artery. The elastica is interrupted with prominent capillaries in these areas. The intima is thickened with organizing thrombus in the reduced lumen. Elastic and van Gieson × 75.

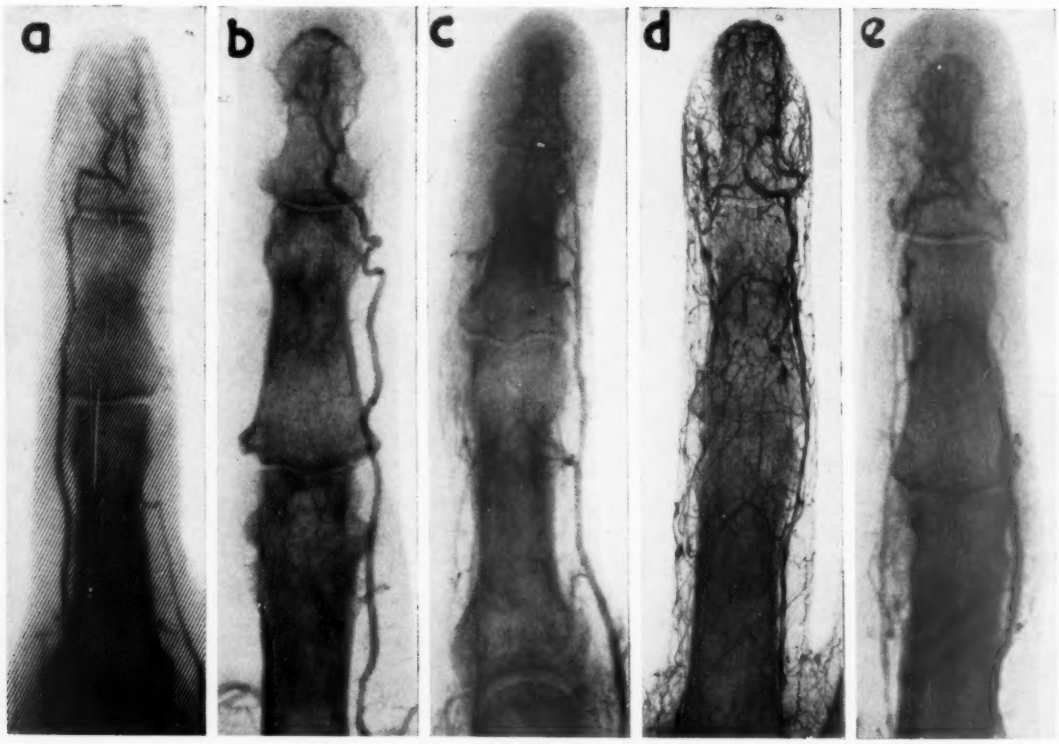

Fig. 4.—Details from arteriograms:

(*a*) Case 2. Little finger. (*b*) Case 4. Ring finger. (*c*) Case 6. Index finger. (*d*) Case 8. Middle finger. (*e*) Case 11. Ring finger.

within the reduced lumen. The elastica had undergone segmental interruption, and capillaries were prominent in the areas of elastic deficiency.

Case 3, a woman aged 55, had nodular rheumatoid arthritis which started in 1955. After various forms of therapy, treatment with prednisolone was started in 1956, the dosage subsequently ranging between 10 and 45 mg. daily, according to disease activity. The only clinical sign of digital arterial disease was the appearance in 1960 of nailfold thrombotic lesions in the index, middle, and ring fingers of each hand. Reactive hyperaemia was normal. The D.A.T. was positive, 1 : 1,024. Arteriography (Fig. 6*a*) showed a constant deformity at the radial end of the deep palmar arch; the radial pollicis was obliterated 2 mm. from its origin and there was segmental blocking of the ulnar pollicis. The radial indicis and ulnar digiti quinti were also incomplete and in each case a collateral artery was seen crossing the middle phalanx. Pulp filling was, however, present, though a little unequal.

Case 4, a man aged 49, had had rheumatoid arthritis for 20 years. Rheumatoid nodules were present. The D.A.T. was positive, 1 : 256. Treatment with cortisone 87·5 mg. daily was started in May, 1957, and changed in May, 1958, to prednisolone 15 mg. daily. The only suggestion of vascular disease was his complaint (on direct questioning) that during the winter of 1959-60 the right foot was sometimes colder than the left. There were no symptoms referable to the hands, which, apart from the arthritis, were clinically normal, as was the reactive hyperaemia. There was, nevertheless, occlusion of the ulnar vessels of the ring and little fingers, and impaired pulp filling in the ring finger (Fig. 4*b*).

Case 5, a man aged 80, had rheumatoid arthritis which started about 1955. Treatment with prednisolone, 10 mg. daily, was started in 1957. In 1958, 2 months after withdrawal of the drug, there was an acute flare of the arthritis, accompanied by pericarditis; this was treated with cortisone 100 mg. daily, reverting to prednisolone 20 mg. daily in February, 1959. He

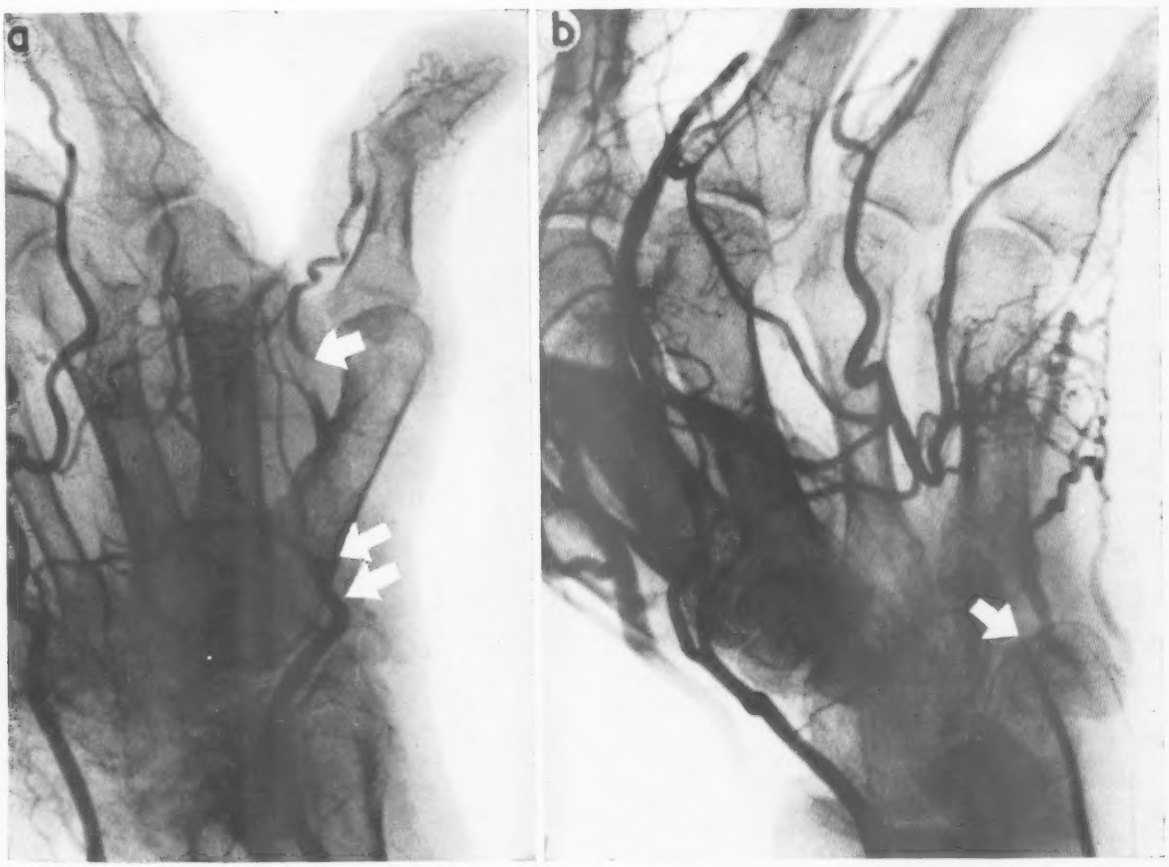

Fig. 6.—Parts of arteriograms.

(*a*) Case 3. Arrows indicate a deformity at the radial end of the deep palmar arch, obliteration of the radial pollicis artery 2 mm. from its origin and segmental blocking of the ulnar pollicis.

(*b*) Case 9. Obliteration of digital arteries and (arrowed) ulnar artery

subsequently developed subcutaneous nodules. The D.A.T. was positive, 1 : 256. In June, 1959, he complained of numbness of the feet which were cold with weak but not absent dorsalis pedis and posterior tibial pulses. Tactile and vibration sense was impaired in the feet and later there was loss of knee and ankle jerks. In August, 1960, an ischaemic lesion was noted on the right index finger. Sensory impairment developed in the fingers with purpura on the wrists. Reactive hyperaemia was normal. Arteriography showed severely impaired blood supply to all the digits except the little finger, and in that finger tortuosity and irregular calibre indicated arterial disease. A biopsy taken from the radial side of the index finger did not, unfortunately, include the main digital artery, but some small vessels showed collagenous intimal thickening, while others appeared normal.

Case 6, a woman aged 43, had had rheumatoid arthritis for one year only, which was remarkable for the striking involvement of the flexor tendons of the fingers, inflammation of which caused the skin to become tethered down, so as to present a picture not unlike scleroderma. The diagnosis of rheumatoid arthritis was, however, confirmed by clinical and radiological evidence of primary joint involvement and erosion of subchondral bone, and was supported by the fact that the patient's identical twin had typical sero-positive rheumatoid arthritis. The patient suffered with cold hands on exposure to cold, but in a hot environment they became pink and warm. Reactive hyperaemia was normal. In addition, she had a sensory neuritis involving the 4th and 5th fingers of the left hand, and also the trigeminal nerve on one side. Another unusual feature was the well-attested history of malignant hypertension with papilloedema 2 years previously, which resolved spontaneously. No nodules were observed in this patient. The D.A.T. was positive, 1 : 16. The arteriogram, performed before treatment with prednisolone was started, showed some of the digital arteries to be irregular and tortuous, with occlusion of the radial index and ulnar digiti quinti, and a collateral vessel crossing the second middle phalanx (Fig. 4*c*). Pulp filling was deficient.

Case 7, a man aged 51, had a 20-year history of uncomplicated rheumatoid arthritis. In September, 1960, he developed bilateral pleural effusions for which no cause was found other than the rheumatoid disease, together with patchy erythema on the trunk with areas of depigmentation and atrophy. The nature of the rash was uncertain, although it bore some resemblance to both lupus erythematosus and dermatomyositis. At the same time his hands became intermittently blue and cold, together with an exacerbation of his arthritis. Thrombotic fingernail lesions were now noted, but reactive hyperaemia was normal. There were no nodules. The D.A.T. was positive, 1 : 128. L.E. cells were not found. He had not received steroid treatment. The arteriogram showed digital artery obstruction with inadequate pulp filling, and a collateral vessel crossing the middle phalanx of the index finger.

Case 8, a man aged 54, had a 12-year history of rheumatoid arthritis and subsequent diffuse pulmonary fibrosis proceeding to "honeycomb lung". Rheumatoid nodules were present. The D.A.T. was positive, 1 : 256. Treatment with prednisolone 15 mg. daily was started in September, 1959, because of increasing dyspnoea, but the patient died in November, 1960, with pulmonary insufficiency. Digital arteritis was not diagnosed during life, and reactive hyperaemia had been normal, but arterial disease was shown by arteriography performed after death (Fig. 4*d*). (There was more small vessel filling than in arteriograms done during life, which was due to loss of arterial tone.) There was blockage of several large arteries. Histology at several levels of each main vessel from the 2nd and 3rd fingers showed fibro-elastic thickening of the intima and some reduplication of the elastica, which was incomplete (Fig. 7*a* and *b*, opposite).

There had been no clinical suggestion of mesenteric arteritis, but Fig. 7*c* shows a mesenteric artery where a similar picture is seen.

Case 9 illustrates that digital vascular disease may proceed to gangrene. This 53-year-old man's nodular rheumatoid arthritis started in 1949, and in 1957 he developed a peroneal and ulnar neuritis, together with a macular erythematous and purpuric rash and skin nodules, biopsy of which showed perivascular infiltration with eosinophils and polymorphs suggestive of polyarteritis nodosa. Treatment with corticosteroid hormones (oral hydrocortisone, triamcinolone, and later methyl prednisolone) was then started. The following year he had transient episcleritis. The D.A.T. was positive, 1 : 128. In 1960, the left index finger became cold and blue, and the tip became gangrenous (Fig. 8, opposite).

Reactive hyperaemia was also delayed in the 3rd and 4th digits (4 and 7 sec. compared with 2 sec. in other digits). Brachial arteriography showed obliteration of the ulnar artery and of all the digital vessels except those of the thumb (Fig. 6*b*). The gangrenous finger-tip was subsequently amputated: Fig. 9 (opposite) shows the histological appearance of a digital artery.

Certain features of this case, namely the skin lesions with a paucity of erosive changes radiologically, indicate that one is here on the difficult terrain between classical rheumatoid arthritis and polyarteritis nodosa.

Polyarteritis nodosa may involve the digits. Fig. 10*a* (overleaf) shows the *post-mortem* arteriogram of the foot of a woman with polyarteritis nodosa presenting with neuritis, who later developed mesenteric vascular occlusion, from which she died. She did not have rheumatoid arthritis. The arteriogram demonstrates blockage of several vessels. Histology of the digital toe vessels shows fibrinoid necrosis in the walls associated with inflammatory cells (Fig. 10*b*).

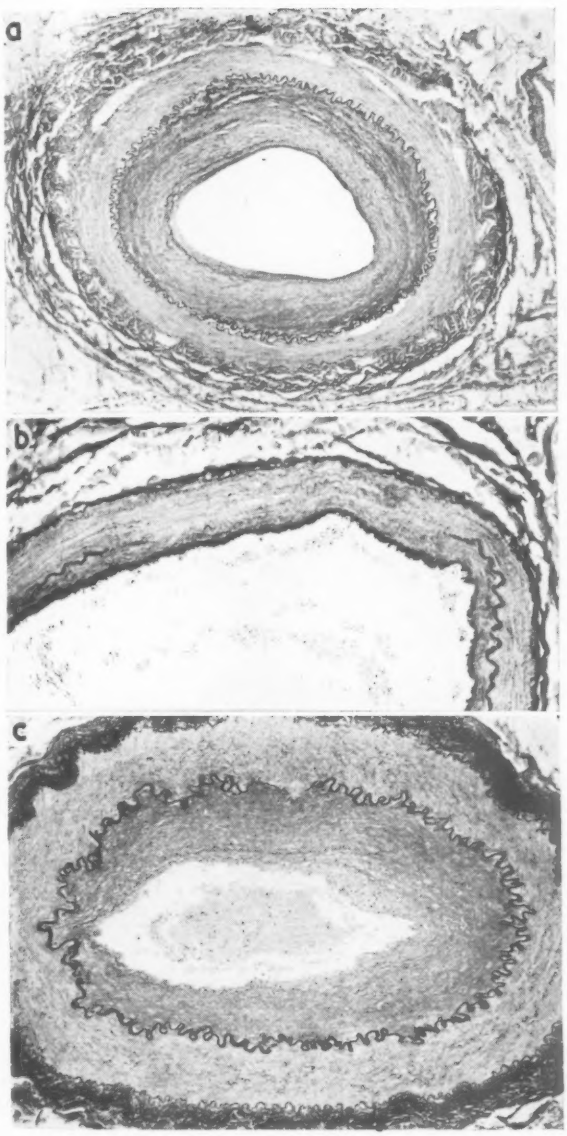

Fig. 7.—Case 8.

(*a*) Digital artery. Fibro-elastic, concentric intimal thickening, with areas of reduplication of internal elastic lamina. Elastic and van Gieson × 66.

(*b*) Part of digital artery, showing segmental interruption of elastica. Elastic and van Gieson × 132.

(*c*) A mesenteric artery. Concentric intimal thickening with occasional interruptions of elastica. There is an abnormally thick adventitia. Elastic and van Gieson × 132.

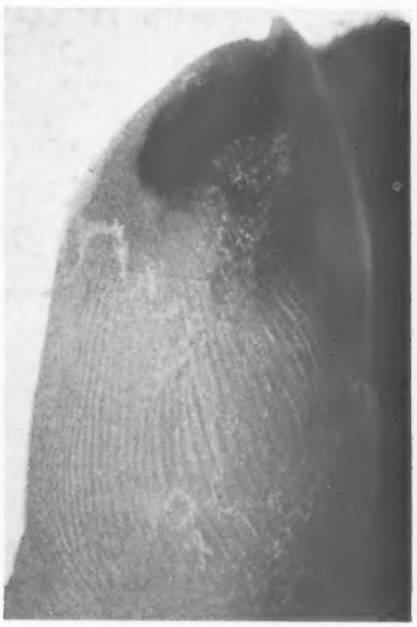

Fig. 8.—Case 9. Gangrenous left index finger.

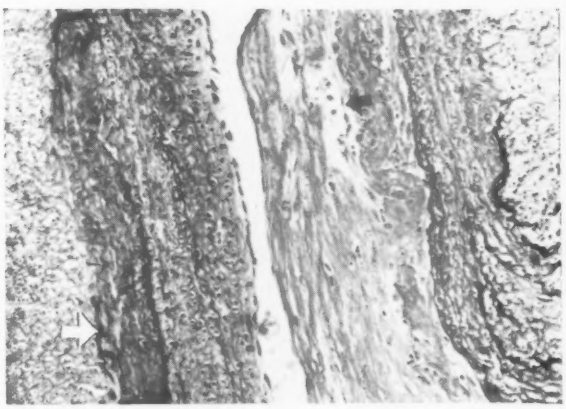

Fig. 9.—Case 9. Longitudinal section of digital artery. The lumen is a central, longitudinal slit, with laminated collagen on either side of it, in which new fibro-muscular elements can be seen on the left-hand side of the photograph. The original internal elastica has been interrupted (white arrow), and two incomplete laminae are visible inside it, separated from each other by loose collagen. Note capillary (black arrow) within the thick, intimal collagen. Elastic and van Gieson × 132.

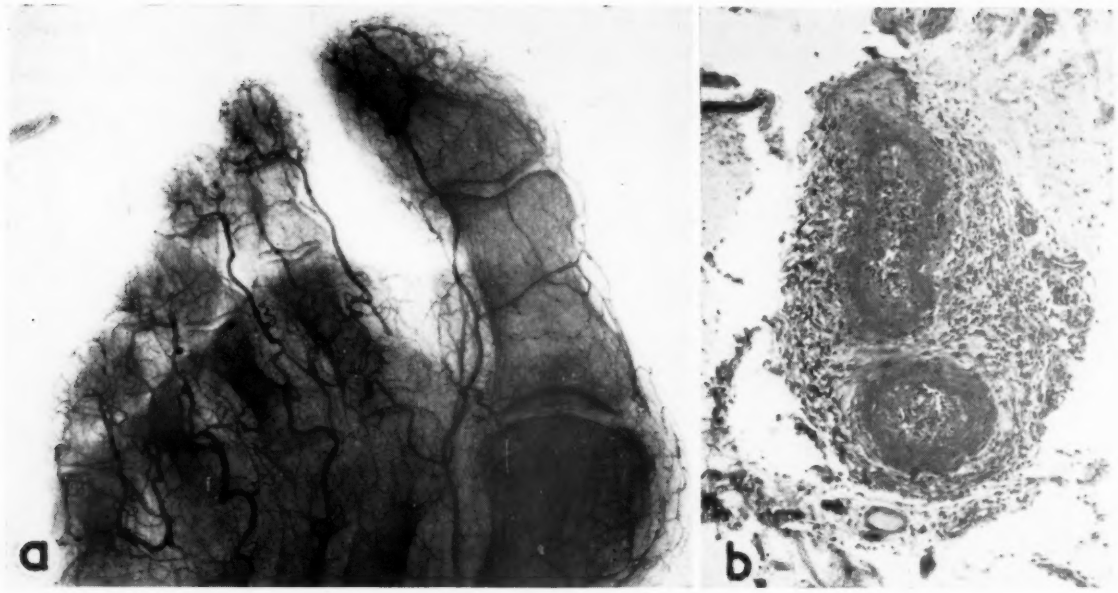

Fig. 10.

(*a*) Post-mortem arteriogram of the foot of a patient with polyarteritis nodosa, showing blockage of several vessels.

(*b*) Branches of digital artery from the same case. There is thrombosis in the lumina, fibrinoid necrosis of the mediae, and inflammatory infiltrate in the adventitiae.
Haematoxylin and eosin. × 100.

The last two cases of rheumatoid disease also show diffuse arteritis and have striking clinical similarities.

Case 10, a man aged 48, had rheumatoid arthritis which started in 1953. In October, 1958, treatment with prednisolone 10 mg. daily was started, and in 1959 the patient developed sensory and motor peripheral neuritis of all limbs, episcleritis, and ulceration of the legs. Rheumatoid nodules were present. The D.A.T. was positive, 1 : 128. A single nail-edge thrombotic lesion was now seen, and reactive hyperaemia was delayed in several fingers up to a maximum of 20 sec., though the skin of the hands and fingers was warm and dry. The arteriogram (Fig. 11) showed considerable variation in arterial calibre and blockage of all the digital arteries, except the ulnar vessels of the thumb, middle, and ring fingers. Pulp filling was present in these three digits only. This patient subsequently died after two laparotomies for mesenteric arteritis, and at autopsy a recent myocardial and several recent renal infarcts were also present. Unfortunately digital vessels were not obtainable for histology. Fig. 12 (*a*, *b*, opposite) shows two mesenteric arteries, one with a bland intimal thickening, the other with fibrinoid necrosis of part of the wall associated with oedema and intense inflammatory reaction, the characteristic picture of polyarteritis nodosa. Both types of lesion were also seen in the adrenal, testis and coronary vessels.

Fig. 11.—Case 10. Brachial arteriogram.

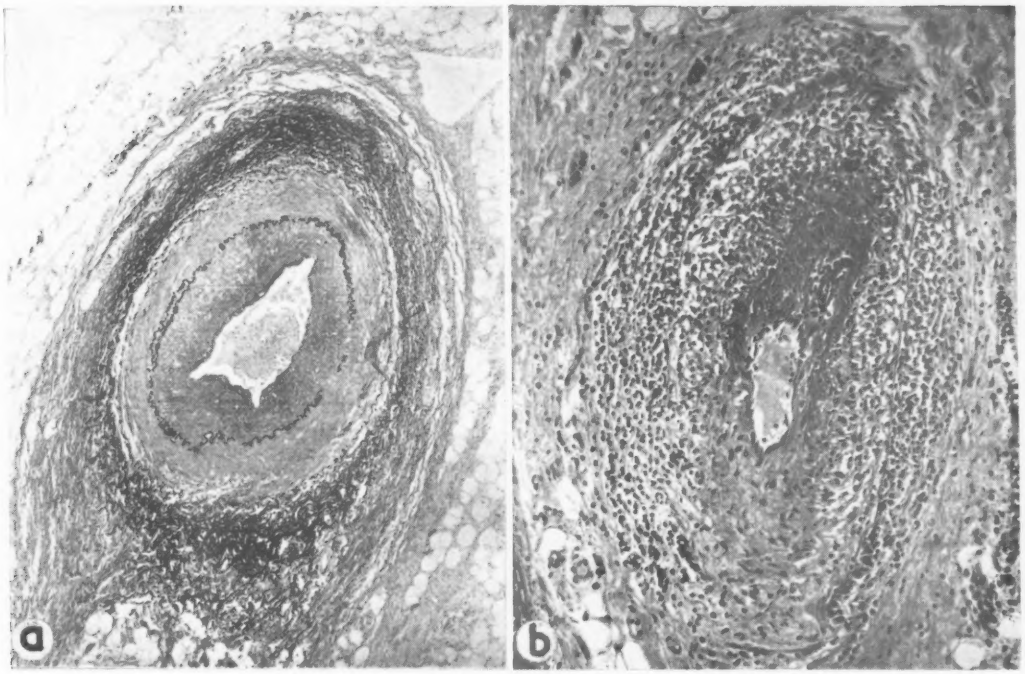

Fig. 12.—Case 10.

(*a*) Mesenteric artery, showing concentric intimal thickening, with interruption of internal elasticae Elastic and van Gieson × 31.

(*b*) Mesenteric artery, showing fibrinoid necrosis and inflammatory cells. Haematoxylin and eosin. × 50.

Case 11, a man aged 59, had rheumatoid arthritis which began in 1951. In October, 1956, treatment was started with cortisone 75 mg. daily. In January, 1960, he complained of paraesthesiae in the right leg, and, in February, of impaired sensation in both feet, followed by bilateral foot drop. He was now found to be diabetic, with glycosuria and a fasting blood sugar of 229 mg. per cent., controlled by an 800-calorie diet and Lente insulin 20 units daily. Examination at this time showed severe generalized rheumatoid arthritis with subcutaneous nodules, peripheral neuritis involving the feet and hands, and haemorrhagic vesicles over the lower legs, but no digital vascular lesions. The D.A.T. was positive, 1 : 1,024. Reactive hyperaemia was slightly delayed in the fourth finger of the left hand only (4 sec., all other digits being 2 sec.).

Arteriography demonstrated some pulp filling in all digits, but the vessels showed abnormal variation in calibre and tortuosity, and there was some blockage in the radial artery of the index finger and both arteries of the ring finger (Fig. 4*e*); 10 days after this film was taken this patient also had mesenteric infarction necessitating excision of gangrenous intestine, which he fortunately survived. Fig. 13 shows the histology of a mesenteric artery.

Calf-muscle biopsy showed some foci of muscle necrosis and collagenous intimal thickening in small arteries, with interruption of the internal elastic lamina.

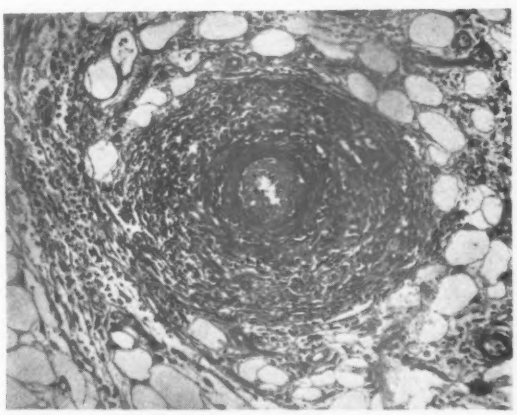

Fig. 13.—Case 11. Small mesenteric artery. The lumen is reduced, a second elastica is incompletely formed inside thickened intimal collagen, and the original elastica is interrupted. Inflammatory cells are largely in the adventitia. Elastic and van Gieson × 31.

Discussion

In this series of brachial arteriograms, no characteristic anatomical pattern of rheumatoid arteritis

has emerged. Any artery in the hand or digits may be involved, though the blood supply of the thumb appears to be less vulnerable than that of the fingers. The radiological lesions are irregularity, narrowing, or obliteration of the arterial lumen, sometimes with opening of collateral vessels. We have not observed post-stenotic dilation nor arterial dilation near bone erosions as reported by Virtama (1959), but his procedure of *post-mortem* arteriography, with magnification of the abundant filling obtained in small vessels, allowed more observation of detail than is possible with arteriograms performed during life.

The clinical features of our cases are summarized in the Table. The significance of these features is limited because it was in fact the presence of some of them which led to arteriograms being done. We seem to have encountered a preponderance of males (9 to 2) with digital arteritis. All the patients were over 40 years of age. The differential agglutination test was positive in all, sometimes strongly so, and nine of the eleven had subcutaneous nodules. L.E. cells were looked for in all the patients, but were not found. Ischaemic digital lesions were seen in only seven of the eleven cases and similarly only five of the eleven had abnormal reactive hyperaemia: one of the most impressive findings of this study has been the demonstration of digital arteritis in some patients with clinically normal hands and normal reactive hyperaemia. Peripheral neuritis was found in seven cases, associated in all but one instance with ischaemic digital skin lesions. There was evidence of visceral involvement in seven cases, though in some instances the connexion with rheumatoid arthritis is questionable.

Most of the patients had received corticosteroids because of severe rheumatoid arthritis, but not Cases 6 and 7: in Case 2 the symptoms of digital ischaemia preceded steroid treatment. We cannot contribute to the problem of corticosteroid therapy as a possible aetiological factor in the development of arteritis except to confirm previous findings (Bywaters, 1957) that arteritis may appear in the absence of steroid treatment.

The histological appearances of the digital arteries suggest an intermittent, progressive collagen increase in the intima, with reduction of lumen, sometimes followed by total occlusion due to thrombosis. No acute arteritis was seen in any of these digital arteries, and although there was elastic

TABLE

CLINICAL FEATURES OF ELEVEN CASES OF RHEUMATOID ARTHRITIS WITH DIGITAL ARTERITIS SHOWN BY ARTERIOGRAPHY

Case	Sex	Age (yrs)	Differential Agglutination Titre	Sub-cutaneous Nodules	Digital Lesions	Reactive Hyperaemia	Peripheral Neuritis	Visceral Involvement	Steroids (yrs)
1	M	57	1 : 16	+	+	Abnormal	+	0	2
2	M	50	1 : 64	+	+	Abnormal	+	0	4 mths*
3	F	55	1 : 1,024	+	+	Normal	0	0	4
4	M	49	1 : 256	+	0	Normal	0	0	3
5	M	70	1 : 256	+	+	Normal	+	Pericarditis	2
6	F	43	1 : 16	0	0	Normal	+	Previous hypertension with papilloedema	0
7	M	51	1 : 128	0	+	Normal	0	Pleural effusions	0
8	M	54	1 : 1,024	+	0	Normal	0	Pulmonary fibrosis Mesenteric arteritis	1
9	M	53	1 : 128	+	Gangrene	Abnormal	+	Rash Episcleritis	3
10	M	48	1 : 128	+	+	Abnormal	+	Leg ulcers Episcleritis Mesenteric arteritis Myocardial infarcts Renal infarcts	1½
11	M	59	1 : 1,024	+	0	Abnormal	+	Leg ulcers Mesenteric arteritis Muscle arteritis	3

* But Raynaud's phenomenon antedating steroid therapy.

interruption, this did not usually cover a large segment of the vessel. However, as pointed out formerly (Bywaters, 1957: Case 2), there may be signs of previous adventitial reaction consisting of circumferential deposits of haemosiderin almost all round the external elastic lamina together with the presence of capillaries within the media. Furthermore, the visceral arteries may show, in the same person, a bland obliterative endarteritis at one place, but occasionally acute inflammatory arthritis elsewhere (Cases 10 and 11). It is difficult to believe that there is not some connexion between these two types of arteritic change, and it seems possible that an acute arteritis of the polyarteritis nodosa type present at one point in the vessel might well lead distally to an obliterative type of change, and perhaps also to thrombosis, both at the site of acute disease or in the secondarily occluded vessel. In Case 2 thrombosis appears to have started peripherally, as shown by multiple sections beyond the obliterated segment. Histological changes along the course of a diseased vessel have yet to be studied in detail; the topographical and temporal relation of the acute arteritis undoubtedly present in some of these patients to the much more commonly observed intimal thickening has yet to be worked out.

How these arteritic lesions are produced is unknown, but a direct rôle of rheumatoid factor is suggested by the recent demonstration of Hess and Ziff (1960) of its binding to blood elements and vessel walls. The significance of arteritis, and the extent to which it is an integral part of the rheumatoid inflammatory process, are still quite speculative.

Summary

Brachial arteriography has been used to investigate the digital circulation in eleven patients with rheumatoid arthritis, in all of whom (except one in whom arteriography was performed at autopsy) there was some reason to suspect the presence of digital arterial disease. In all there was a varying degree of vascular occlusion or distortion, and histological examination has shown a non-specific arterial lesion with intimal thickening. Visceral arteritis was sometimes present with lesions indistinguishable from either acute or healed polyarteritis nodosa. In two patients with early rheumatoid arthritis, and no signs of peripheral vascular disease, arteriography was normal.

REFERENCES

Aronoff, A., Johnson, L., and Dworkin, S. (1960). *Canad. med. Ass. J.*, **83**, 58.

Ball, J. (1954). *Ann. rheum. Dis.*, **13**, 277.

Bywaters, E. G. L. (1957). *Ibid.*, **16**, 84.

Cruickshank, B. (1954). *Ibid.*, **13**, 136.

Edwards, E. A. (1960). *Amer. J. Surg.*, **99**, 837.

Graef, I., Hickey, D. V., and Altmann, V. (1949). *Amer. Heart J.*, **37**, 635.

Hess, E. and Ziff, M. (1960). *Cited by* Odone, Wilson, and Engleman (1960).

Levin, M. H., Rivo, J. B., Scott, W., Figueroa, W. G., Fred, L., and Barrett, T. F. (1953). *Amer. J. Med.*, **14**, 265.

Lynn, R. B., Steiner, R. E., and Van Wyk, F. A. K. (1955). *Lancet*, **1**, 471.

Nyström, G. (1953). *Ann. Med. intern. Fenn.*, **42**, 52.

Odone, D. T., Wilson, A. F., and Engleman, E. P. (1960). *Bull. rheum. Dis.*, **11**, 229.

Ogryzlo, M. A. (1953). *Ann. rheum. Dis.*, **12**, 323.

Pickering, G. W. (1933). *Brit. med. J.*, **2**, 1106.

Schmid, F. R., Cooper, N. S., Ziff, M., and McEwen, C. (1961). *Amer. J. Med.*, **30**, 56.

Sokoloff, L., Wilens, S. L., and Bunim, J. J. (1951). *Amer. J. Path.*, **27**, 157.

Virtama, P. (1959). *Acta rheum. scand.*, **5**, 304.

DISCUSSION

DR. J. J. BUNIM (*Bethesda, Md*): I thoroughly enjoyed this paper and cannot add anything substantial to it. It is very interesting that all of the eleven patients had a positive sheep cell agglutination test and that nine of them had nodules. The association of the rheumatoid factor with vasculitis has been observed previously and is well confirmed by this study. I think it is very important to distinguish between digital arteritis and polyarteritis nodosa. I realize that it was impossible to do so in this study, but nevertheless we see patients with these thrombotic digital lesions, who are immediately suspected to have polyarteritis nodosa. A grave prognosis is given and steroid therapy instituted, but it is found that these patients do not really have polyarteritis nodosa, because the course of the disease is rather benign and they do much better than those who have a thrombosis as part of polyarteritis nodosa. I should like to congratulate Dr. Scott and his group for such a constructive study and hope to emulate them by adopting these studies as soon as I return home.

PROF. J. H. KELLGREN (*Manchester*): I should like to congratulate Dr. Scott on the beautiful illustrations. I have one relevant observation: there are patients who have arteritis of this type, but no arthritis or joint disease, who yet have positive rheumatoid factor tests. We had the opportunity in Manchester of studying over twenty patients of this type, mostly middle-aged women and a few men, who presented with acute secondary Raynaud's phenomenon. There was no clinical or radiological evidence of joint disease, but nevertheless over 50 per cent. had positive tests. This raises the question whether there is not a rheumatoid type of arterial disease which may or may not be associated with joint disease, and also the question of the prevalence of positive tests and rheumatoid arthritis in the general population. The correlation of the factor with joint disease in the

population as a whole is relatively low, but we do not know to what extent other pathological processes are associated with this factor.

DR. BASIL STRICKLAND (*London*): As a guest radiologist I really have no right to speak, but should like to add my congratulations to the radiologists. I think one may assume that arteriograms in such advanced cases will show changes, whatever the diagnosis may be. Arteriograms of really early cases with such good quality pictures might be much more informative.

The second point is rather technical. I was very interested to hear that these arteriograms were carried out with a local anaesthetic. I would prefer to do them under a general anaesthetic. I think that if you inject the brachial artery under local anaesthesia and later on give a general anaesthetic you get a different picture. It is often difficult to determine the degree of spasm under local anaesthesia with this particular artery, but with general anaesthesia that spasm can often be obviated and more definite conclusions drawn.

DR. STEINER: I will confine myself to answering Dr. Strickland's question. I have been interested in this matter for some time. We originally investigated Raynaud's disease, and in true cases of Raynaud's phenomenon we found that a general anaesthetic is undoubtedly essential. These patients are of course sensitive to puncture, so that the artery goes into spasm, and, as Dr. Scott said, the first few patients were studied under general anaesthesia. However, we later found we could manage with a local, and this has been so much simpler with "Hypaque", which is less toxic than the original dye used. In one case of this series there was considerable arterial spasm following injection, and two other cases of Raynaud's disease not reported also went into spasm.

If you suspect vascular spasm of the Raynaud type you should give a general anaesthetic. However, in cases of rheumatoid arthritis local anaesthesia will suffice.

In cases of vascular spasm the whole arterial tree is involved and the appearance of local organic blocking and collateral circulation which was seen in these cases cannot be observed.

PROF. BYWATERS: I am glad to endorse Dr. Bunim's comment about polyarteritis nodosa. Obviously, classical polyarteritis is a different sort of picture. What has worried me since our first publication in 1957, is that these patients with rheumatoid obliterating endarteritis sometimes show a fairly large vessel with acute inflammation. We do not yet know the spatial relationship along the length of the artery. Is there acute inflammatory disease with secondary bland obliterating endarteritis further up the vessel, or is the acute lesion secondary in some way to the obliterative lesion? I think clinically we can recognize classical polyarteritis nodosa, but we still know little about the incidence of isolated and healed arteritis and much more information is wanted about *formes frustes* of polyarteritis, such as are found without clinical signs after appendectomy or amputation of the cervix. The Rose-Waaler test may be of some help in differentiating classical polyarteritis and the obliterating arteritis of rheumatoid arthritis.

DR. SCOTT: With regard to Dr. Strickland's first point, it was in fact because of abnormal arteriograms in the patients who showed some indication of arterial disease that we investigated two further cases with early rheumatoid arthritis, in both of whom the arteriogram turned out to be normal. Such information as we have, therefore, suggests that arteritic changes tend to be late. We do not think that vascular spasm is an important factor in the abnormal films, because the picture is usually one of rather abrupt blockage often with collateral circulation, and histology has shown the presence of organic occlusion.

Digital arteriography may be of practical value in the individual case. For example, the gangrenous index finger illustrated (Case 9) has since been amputated, and on clinical grounds the elective site of amputation made was through the second metacarpal bone, allowing apposition of the thumb and middle finger. When arteriography showed that the blood supply of all the other fingers was so bad, however, it was decided to amputate through the proximal interphalangeal joint, leaving as much as possible of the index finger in case the other fingers should be lost.

Artérite digitale dans la maladie rhumatismale

RÉSUMÉ

On étudia au moyen de l'artériographie brachiale la circulation digitale chez onze malades atteints d'arthrite rhumatismale; chez tous ces malades (sauf un, chez qui l'artériographie fut faite à l'autopsie) il y avait une raison pour soupçonner l'existence d'une affection artérielle des doigts. Chez tous on trouva des occlusions et des déformations vasculaires d'intensité variable et l'examen histologique révéla des lésions artérielles non spécifiques avec un épaississement de l'intime. L'artérite viscérale fut quelquefois présente et les lésions observées ne se distinguaient pas de celles qu'on trouve dans la polyartérite noueuse aiguë ou guérie. Chez deux malades avec une arthrite rhumatismale précoce et sans signes de maladie vasculaire périphérique, l'artériographie fut normale.

Arteritis digital en enfermedad reumatoide

SUMARIO

Se investigó por medio de arteriografía braquial la circulación digital de once enfermos con artritis reumatoide; en todos ellos (excepto uno, en quien la arteriografía se praticó en autopsia) existía alguna razón para sospechar la existencia de enfermedad arterial de los dedos. En todos existía oclusion y deformación vascular en grado variable, y exámenes histológicos mostraron la presencia de una lesión arterial no específica con engrosamiento de la íntima. En algunos casos se observó la presencia de arteritis visceral con lesiones indiferenciables de las halladas en poliarteritis nodosa, aguda o curada. En dos enfermos con artritis reumatoide incipiente, y sin signos de enfermedad vascular periférica, la arteriografía fué normal.

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EPIDEMIOLOGY OF THE SHEEP CELL AGGLUTINATION TEST

BY

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From the Rheumatism Research Centre, Manchester University, and the Empire Rheumatism Council's Field Unit

Recent research into the nature and significance of rheumatoid serum factors has been largely immunological and biochemical. The epidemiology of these components is virtually unknown. During recent years we have had the opportunity of studying several population samples, and data from these surveys have now been gathered and are presented with particular reference to the epidemiology of the serum factor which reacts with sheep cells sensitized by a rabbit anti-sheep haemolysin.

Material and Methods

The following populations have been investigated during the last 7 years and are listed below in roughly chronological order:

(1) *Leigh.*—Two surveys have been conducted in this mining and industrial borough in Lancashire, England:
   (*a*) A 1 in 10 random sample drawn from the electoral roll, comprising 204 males and 277 females aged 55-64 years;
   (*b*) A 1 in 30 random sample, also drawn from the electoral roll, of subjects aged 15 years or more, comprising 768 males and 846 females, including part of (*a*).

   Some observations on the Leigh population have already been published (Kellgren and Lawrence, 1956; Lawrence and Ball, 1958; Lawrence and Bennett, 1960).

(2) *Glamorgan.*—A sample comprising 100 males and 100 females aged 55-64 years from the Vale of Glamorgan, a farming area in South Wales. This is approximately a 1 in 3 sample and was chosen at random from a census undertaken by the Pneumoconiosis Research Unit.

(3) *Annandale.*—A sample comprising 105 males and 101 females aged 55-64 years from the rural area of Annandale in Southern Scotland. This is approximately a 1 in 4 sample and was chosen at random from a private census undertaken by Cochran, Clayson, and Fletcher (1957) in connexion with a chest survey.

(4) *Rhondda.*—A stratified random sample comprising 600 males aged 35-64 years and 200 females aged 55-64 years from the Rhondda Fach, a coal mining area in South Wales. The males were stratified so that there were 100 miners and 100 non-miners in each decade. This represents approximately the proportions of these workers in the area and is roughly a 1 in 7 sample of the total in each decade. Selection within the strata was random, and was taken from a census by the Pneumoconiosis Research Unit.

(5) *Rotterdam.*—A random sample comprising 166 males and 154 females aged 55-64 years from the City of Rotterdam, The Netherlands. These subjects were contained in a larger sample of the population aged 15-64 which was selected by taking every 50th card from the municipal register; if the person chosen was not in the 15-64 age group, the next card was taken and so forth.

(6) *Wensleydale.*—This was an area sample of 509 males and 553 females aged 15 years or more in the rural district of Wensleydale in Northern England. It included half the main town of Hawes and half the farms and villages in the dale.

(7) *Heinola.*—An approximately 1 in 2 random sample comprising 175 males and 214 females, aged 55-64 years, from the population of a rural area 70 miles North of Helsinki, Finland. The majority of the subjects in the sample lived in a village and worked in a hardboard factory. The blood samples taken were tested by various methods. In 53 of the males and 64 of the females, the blood samples were too small to allow a S.C.A.T. test to be performed, but the results obtained by other methods suggest that the sample tested by the S.C.A.T. is representative.

The sensitized sheep cell test was performed as previously described (Ball, 1950), a titre of 1 in 32 after 18 hrs' incubation being defined as a minimum positive result (Kellgren and Ball, 1959). The haemolysin used was either prepared by us in rabbits or obtained from Cappel Laboratories. Secular errors have been minimized by standardizing the sensitivity of the test against a series of human sera of known agglutinating activity. Titres are expressed below as the reciprocal of the serum dilution; a titre of <4 signifies no agglutination detected within the range of serum dilutions tested (1 in 4 to 1 in 4,096).

The clinical and radiological methods used have been described elsewhere (Kellgren and Lawrence, 1956; Lawrence and Ball, 1958).

Results

Geographic Variations.—These have been studied only in the 55- to 64-year age group, since in most areas this was the only age range tested. Among seven population samples the proportion of positive titres varied between 1·6 and 5·4 per cent. (Table I). The mean prevalence of sero-positive subjects was significantly greater in urban than in rural areas ($p = <0·01$).

In the urban populations, positive titres were equally divided between males and females. In the rural samples no definite sex preponderance emerged, though the number of positive tests was small, and a more detailed study of other age groups in the Wensleydale population (see below) did reveal a lower prevalence of positive tests in males aged over 54 years.

Age and Sex Distribution of Positive Tests.—This was studied in the Leigh (*b*) and Wensleydale populations; in addition, the age distribution of

TABLE I

PREVALENCE OF POSITIVE TESTS IN URBAN AND RURAL POPULATIONS AGED 55 TO 64 YEARS

Sample		Geographical Latitude	Total Available Sample			Total Tested			Titre 32 or More					
			Males	Females	Both Sexes	Males	Females	Both Sexes	Males		Females		Both Sexes	
									No.	%	No.	%	No.	%
Rural	Heinola ..	61° N.	175	214	389	104	123	245	3	2·9	1	0·8	4	1·6
	Annandale ..	55° N.	105	101	206	96	91	187	3	3·1	1	1·1	4	2·1
	Wensleydale	54° N.	63	76	139	55	62	117	0	0	3	4·8	3	2·6
	Glamorgan ..	51° N.	100	100	200	88	85	173	2	2·3	4	4·7	6	3·5
	Total ..		443	491	934	343	361	704	8	2·3	9	2·5	17	2·4
Urban	Leigh ..	53° N.	204	277	481	163	187	350	8	4·9	11	5·9	19	5·4
	Rhondda ..	52° N.	200	200	400	177	181	358	11	6·2	7	3·9	18	5·0
	Rotterdam ..	51° N.	166	154	320	138	133	271	6	4·3	7	5·3	13	4·8
	Total ..		570	631	1,201	478	501	979	25	5·2	25	5·0	50	5·1

TABLE II

DISTRIBUTION OF TITRES BY AGE AND SEX IN LEIGH (*b*) AND WENSLEYDALE

Area	Age (yrs)	Males												Females										
		Total Sample	Total Tested	Titre										Total Sample	Total Tested	Titre								
				<4	4	8	16	32	64	128	256	512	⩾32			<4	4	8	16	32	64	128	256	512	⩾3
													No.	%											No.
Leigh	15–24	125	103	81	8	11	3	0	0	0	0	0	0	0	122	99	66	19	9	3	1	0	1	0	0	2
	25–34	131	113	66	24	16	2	1	2	1	0	1	5	4·4	115	97	52	15	19	6	4	0	0	1	0	5
	35–44	127	103	55	27	15	4	1	0	1	0	0	2	1·9	148	119	67	24	14	10	4	0	0	0	0	4
	45–54	169	147	92	24	11	11	4	2	2	1	0	9	6·1	171	140	77	22	15	15	7	1	3	0	0	11
	55–64	102	88	47	26	7	4	1	1	1	1	0	4	4·5	139	101	59	22	10	4	3	1	1	1	0	6
	65+	114	95	55	8	9	9	7	3	3	1	0	14	14·7	151	106	57	18	13	8	5	2	1	1	1	10
	Total	768	649	396	117	69	33	14	8	8	3	1	34	5·2	846	662	378	120	80	46	24	4	6	3	1	38
Wensley-dale	15–24	90	86	73	3	6	2	1	0	0	1	0	2	2·3	79	72	60	7	5	0	0	0	0	0	0	0
	25–34	72	61	48	8	4	1	0	0	0	0	0	0	0	79	70	53	9	4	2	1	1	0	0	0	2
	35–44	95	85	66	9	8	0	2	0	0	0	0	2	2·4	101	94	80	6	6	1	1	0	0	0	0	1
	45–54	108	90	79	5	5	0	0	0	0	0	1	1	1·1	86	78	65	5	5	0	2	1	0	0	0	3
	55–64	63	55	50	2	2	1	0	0	0	0	0	0	0	76	62	46	6	7	0	0	2	0	0	1	3
	65+	81	67	60	4	2	1	0	0	0	0	0	0	0	132	111	90	6	7	1	4	0	1	0	2	7
	Total	509	444	376	31	27	5	3	0	0	1	1	5	1·1	553	487	394	39	34	4	8	4	1	0	3	16
Grand Total	No.	1,277	1,093	772	148	96	38	17	8	8	4	2	39		1,399	1,149	772	159	114	50	32	8	7	3	4	54
	Per cent.		100	70·6	13·6	8·8	3·5	1·6		1·5		0·5		3·6		100	67·2	13·8	9·9	4·4	2·8		1·3		0·6	
		Males and Females																							
Leigh Total	No.	1,614	1,295	758	237	149	79	38		26		8	72												
	Per cent.		100	58·6	18·3	11·5	6·1	2·9		2·0		0·6	5·5												
Wensley-dale Total	No.	1,062	931	770	70	61	9	11		5		5	21												
	Per cent.		100	82·7	7·5	6·6	1·0	1·2		0·5		0·5	2·3												

positive tests was investigated in the males of the Rhondda sample. The results are shown in Tables II and III and Figs 1 and 2. There was a greater overall prevalence of positive tests in Leigh (5·5 per cent.) than in Wensleydale (2·3 per cent.), which confirms in a more representative sample the findings regarding rural and urban populations already described for the 55- to 64-year age group (Table I). In Leigh, positive results occurred with virtually the same frequency in males and females in all age groups. In Wensleydale, however, there was a significantly greater prevalence ($p = <0·05$) of positive tests in females (3·3 per cent.) than in males (1·1 per cent.), mainly because of the absence of positive titres in males aged over 54 years. It will be seen that the prevalence of positive tests in Leigh increased from approximately 1 per cent. in the 15- to 24-year age group to 12 per cent. in subjects aged 65 or over. This increase with age was present in both males and females (Fig. 1). An increase with age was also found in the males in the Rhondda sample and in the Wensleydale females, but in the Wensleydale males there were no positive tests among subjects aged 55 or over (Fig. 2).

In males and females in Leigh, the trend upwards in the prevalence of positive tests with age presented two peaks spaced at an interval of about 20 years (Fig. 1). The differences producing the peaks do not reach statistically significant levels.

TABLE III

DISTRIBUTION OF TITRES BY AGE IN RHONDDA MALES

Age (yrs)	Total Sample	Total Tested	Titre										
			<4	4	8	16	32	64	128	256	512	⩾32	
												No.	%
35–44	200	162	142	8	7	2	1	0	0	2	0	3	1·9
45–54	200	184	166	7	6	2	3	0	0	0	0	3	1·6
55–64	200	179	150	9	6	3	4	3	1	1	2	11	6·1

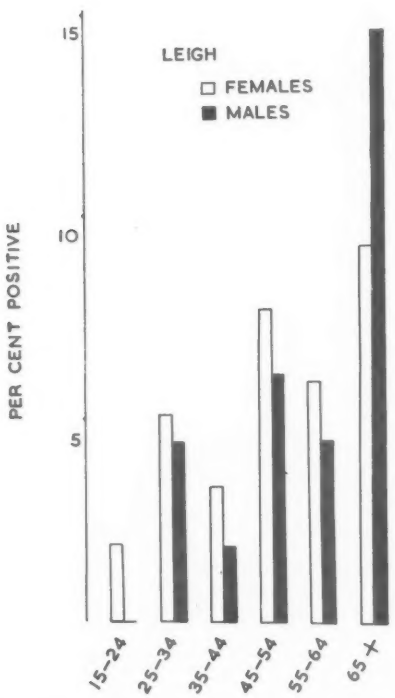

Fig. 1.—Prevalence of positive tests by age and sex in Leigh (*b*).

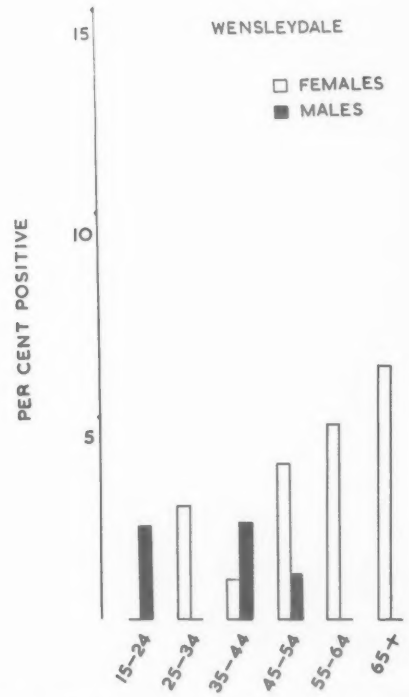

Fig. 2.—Prevalence of positive tests by age and sex in Wensleydale.

Distribution of Titres.—This is shown for the Leigh (*b*) and Wensleydale populations in Table II and Figs 3 and 4. In Leigh, which is the larger sample, the titre distribution follows a simple curve; the curve for Wensleydale is uneven, but there is no definite evidence of bimodality (Fig. 3). In the combined Leigh and Wensleydale sample (Fig. 4) the titre distribution similarly forms a simple curve which is virtually identical in males and females. It can be seen (Fig. 3) that the curve for Leigh (in which there was a higher overall prevalence of positive tests than in Wensleydale) is set at a higher level than the curve for Wensleydale at all agglutination titres. These findings do not suggest a qualitative difference between low and high titre agglutination.

Agglutination of some degree occurred in about 17 per cent. of the Wensleydale sample and in about 40 per cent. of the Leigh (*b*) population.

Genetic Factors.—The possibility that rheumatoid factor is subject to genetic influences was investigated in the Leigh sample by comparing the titre distribution among the first degree relatives (parents, siblings, and offspring) with those of the propositi. All sero-positive individuals in the sample were chosen. The sero-negative propositi included healthy individuals and subjects suffering from rheumatoid arthritis or other diseases. Table IV (opposite) shows that the proportion of sero-positive relatives increases as the titre of the propositi increases above 4. Thus, 12 per cent. of relatives of propositi with a titre of 128 or more were positive as compared with 3 per cent. of relatives of propositi with titres of 4 or less, the difference being significant at the 1 per cent. level. This difference is not likely to be due to differences in the age distribution of relatives in the two titre groups compared (Table V, opposite).

In an attempt to exclude an environmental cause of the observed familial aggregation of sero-positivity, the results in married persons were considered. Among 1,200 married persons, positive titres were found in 4 per cent.; thus, by chance alone, both spouses would be expected to be positive once in 625 couples. In fact, two couples were found in which both husband and wife were positive.

Relation of the Titre to the Diagnostic Criteria of Rheumatoid Arthritis.—This was studied in the combined Leigh (*b*) and Wensleydale sample. The diagnosis of rheumatoid arthritis was based on the American Rheumatism Association's criteria (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), except that

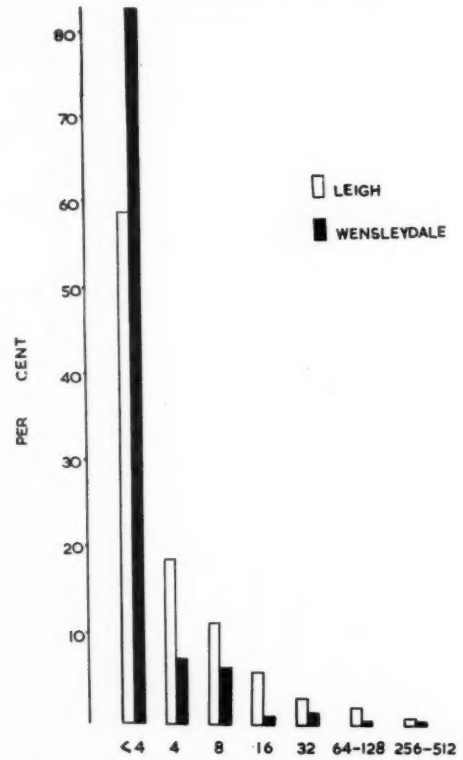

Fig. 3.—Titre distribution in Leigh (*b*) and Wensleydale, all age groups and both sexes combined.

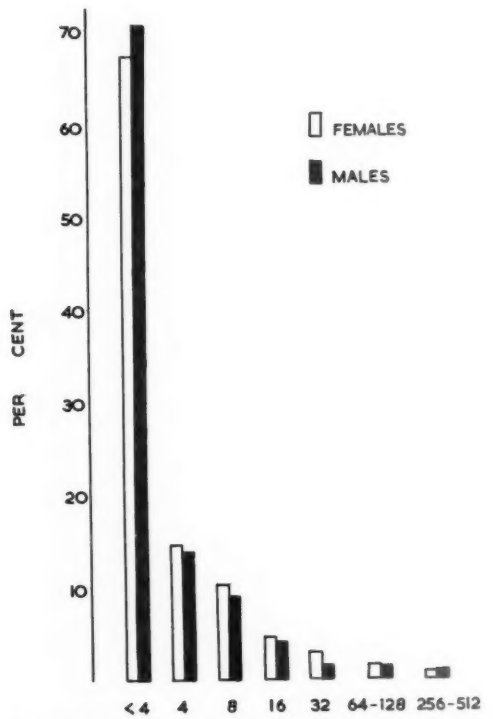

Fig. 4.—Titre distribution in males and females (all age groups) of the combined Leigh (*b*) and Wensleydale samples.

TABLE IV

RELATION OF TITRES IN RELATIVES AND PROPOSITI

Propositi		Relatives						
		Total in Sample	Total Tested	Titre of Those Tested				
				<4	4–16	32–64	128–512	Percentage ⩾32
Titre	<4	363	207	131	71	4	1	3
	4	99	87	64	20	2	1	
	8	42	39	27	10	1	1	6
	16	31	23	8	13	1	1	
	32	158	124	82	29	9	4	10
	64	60	32	21	9	2	0	
	128	59	40	21	15	4	0	12
	256	33	26	14	8	2	2	
	512	11	8	6	1	1	0	

TABLE V

DISTRIBUTION OF RELATIVES BY AGE

Propositi		Relatives										
		Total in Sample	Total Tested	Age of Those Tested (yrs)						Percentages		
				15–24	25–34	35–44	45–54	55–64	65+	45+	55+	65+
Titre	<4–4	462	294	19	60	53	40	76	46	55	38	15
	8–16	73	62	11	13	14	3	8	13	39	34	20
	32–64	218	156	18	23	39	33	17	26	49	28	16
	128–256	103	74	5	17	6	25	12	9	62	28	12

in computing the score the point normally given for a positive S.C.A.T. was excluded; the diagnosis of rheumatoid arthritis was thus in this sense rather more strict than would normally be the case. The results are shown in Table VI. Among the 2,242 persons tested, 93 were sero-positive, but of these only eighteen (19·4 per cent.) had definite or probable rheumatoid arthritis (*i.e.* at least three A.R.A. criteria, not counting the S.C.A.T. point). As expected, the prevalence of definite or probable rheumatoid arthritis increased sharply in the titre groups above 16, a finding which, parenthetically, validates the choice of a titre of 32 as the minimum positive titre in this laboratory.

5 years after the Leigh (*a*) survey was completed, 57 subjects originally aged 55-64 years, were chosen for follow-up. They included the nineteen sero-positive subjects and a sample of 38 sero-negative subjects, each serological group containing clinical

TABLE VI

S.C.A.T. TITRE AND AMERICAN RHEUMATISM ASSOCIATION'S CRITERIA

Titre	Total No.	At Least Three A.R.A. Criteria (not including S.C.A.T. point)	
		No.	Percentage of Total
<4	1,544	54	3·5
4	307	10	3·3
8	210	8	3·8
16	88	3	3·4
<4–16	2,149	75	3·5
32	49	4	8·2
64–128	31	5	16·1
256–512	13	9	69·3
32–512	93	18	19·4

rheumatoid arthritic and non-rheumatoid individuals. Of these, four had died and twelve could not be re-tested. None of the latter had changed clinically. Of the four who died, three were originally S.C.A.T. negative and none of the four had clinical rheumatoid arthritis. It will be seen (Table VII) that twelve of the initially S.C.A.T.-positive and 29 of the initially S.C.A.T.-negative subjects were re-assessed in 1959: Of the seven S.C.A.T.-positive non-rheumatoid subjects two were found to have developed the disease in the interval, but of the 25 S.C.A.T.-negative non-rheumatoid subjects none had developed rheumatoid arthritis. On the other hand, two of four subjects initially classified as suffering from S.C.A.T.-negative rheumatoid arthritis had gone into remission, whereas of the five subjects initially falling in the S.C.A.T.-positive rheumatoid arthritic group, none had remitted—one had in fact deteriorated.

Discussion

The prevalence of positive S.C.A.T. results varied only between 1·6 and 5·4 per cent. in several European population samples aged 55-64 years; there was, nevertheless, a significantly greater prevalence in urban than in rural areas (Table I). This finding was confirmed in a comparison of urban (Leigh) and rural (Wensleydale) samples which included all age groups over 15 years, the difference being particularly marked in males aged over 54 years (Table II). Both males and females in Leigh are exposed to a much heavier industrial pollution of the atmosphere than are the people of Wensleydale. Most of the females in Leigh and Wensleydale are occupied in their homes, but whereas the Leigh males work in mines or in various manufacturing industries, the Wensleydale males are employed mainly in the open air on farms or on the roads and railways. There may thus be a greater occupational difference between urban and rural males than females.

The S.C.A.T. titre appears to be influenced by genetic factors. In Leigh the proportion of positive titres among first-degree relatives increased as the titre of the propositi increased, and was four times greater in relatives of propositi with a titre of 128 or more than in relatives of propositi with titres of 4 or less (Table IV). This familial aggregation did not appear to be due to environmental factors—at least in adult life—as judged by the prevalence of positive titres in spouses. Nor does it appear to depend on the clinical state of the propositus, since we have previously found a similar degree of familial aggregation among relatives of both rheumatoid and non-rheumatoid sero-positive individuals contained in a random sample (Lawrence and Ball, 1958). No similar genetic study of this rheumatoid factor has been reported, but Robecchi and Daneo (1959) and Bremner, Alexander, and Duthie (1959) have performed sheep cell agglutination tests on the serum of relatives of sero-positive and sero-negative rheumatoid arthritics attending hospital. Robecchi and Daneo found that 32·1 per cent. of the relatives of sero-positive rheumatoid arthritics had a titre of 32 or more as compared with 17·3 per cent. of the relatives of sero-negative rheumatoid propositi. Bremner and others (1959) found positive results in 1·8 per cent. of 109 relatives of sero-negative rheumatoid propositi and in 4·4 per cent. of 91 relatives of sero-positive rheumatoid propositi, the difference being statistically non-significant. The low level of sero-positivity found by Bremner and others was not due to the serological method used, since in a small series of serum samples tested concurrently by Bremner and others and by us, essentially similar results were obtained. The failure to find definite statistical evidence of familial aggregation may simply mean that the

TABLE VII

LEIGH 5-YEAR FOLLOW-UP STUDY

1954 Assessment					Re-assessment in 1959				
S.C.A.T. Results	Clinical Rheumatoid Arthritis	Males	Females	Total	Total Re-assessed	S.C.A.T.-Positive		S.C.A.T.-Negative	
						Clinical Rheumatoid Arthritis		Clinical Rheumatoid Arthritis	
						Present	Absent	Present	Absent
Positive ..	Present ..	3	5	8	5	4	0	1	0
	Absent ..	5	6	11	7	2	4	0	1
Negative ..	Present ..	1	4	5	4	0	0	2	2
	Absent ..	17	16	33	25	0	0	0	25
Total		26	31	57	41	6	4	3	28

sample tested by Bremner and others was too small. On the other hand it could mean that their sample was qualitatively different, in the sense that their propositi included a larger number of subjects in which sero-positivity was environmentally rather than genetically determined; there is no evidence that this was the case, but such a circumstance, if it occurred, would obscure evidence of genetic factors. There is suggestive evidence that sero-positivity may in fact be predominantly genetically determined in some and environmentally determined in others. Seropositivity is more common in healthy members of the general population than in those who suffer from, or have a history of, rheumatic disease at the time of the test; and our results indicate that in these healthy subjects the sero-positivity may be genetically determined. On the other hand, among three pairs of identical twins, whose sera were examined by us through the courtesy of Dr. A. St. J. Dixon, the S.C.A.T. was positive in one twin in two pairs and in both twins in the remaining pair, indicating that non-genetic factors may affect the S.C.A.T. titre, causing or preventing the development of a positive test. Furthermore, among rheumatoid arthritics attending hospital, sero-positivity (in our laboratory) may develop long after the onset of the disease (Dixon, 1960). In experimental animals, the S.C.A.T. titre appears to be influenced by both constitutional and acquired factors, since increased S.C.A.T. titres have been induced by injection of certain bacteria, but only a proportion of the animals may react in this way (Lerner, Bloch, and Williams, 1960; Abruzzo and Christian, 1961).

Ziff, Schmid, Lewis, and Tanner (1958) have reported familial aggregation of a serum factor agglutinating tanned sheep erythrocytes coated with human γ globulin (Cohn fraction II); and a similar result was obtained by them with a test which measures the ability of human serum to inhibit the agglutination of sensitized sheep cells. It is, however, uncertain that these tests can be equated with the procedure used by us: absence of inhibition has not been proved to be due of necessity to amounts of agglutinating factor not detectable in the direct test (Vaughan and Good, 1958; Vaughan, 1959); and it is known that sera may sometimes react with human γ globulin but fail to react with sheep cells sensitized with rabbit haemolysin (Peltier and Christian, 1959; Kunkel, Simon, and Fudenberg, 1958). In this connexion it seems important to mention that Goldenberg, Singer, and Plotz (1960) claim to have detected evidence of familial aggregation when sera were examined by sheep cells sensitized by rabbit haemolysin but not when the same sera were tested with reagents utilizing human γ globulin in the form either of Cohn fraction II or incomplete anti-D serum.

In the urban samples, positive S.C.A.T. results were distributed equally between males and females; in both sexes the proportion of positive titres was greater in the older age groups. This relation to age was not due to the selective survival of sero-positive individuals, since the absolute number of positive tests was also greater in the older age groups. The observed difference with age could, however, be due to the one-time operation of factors which leave a permanently raised titre, but which are currently dying out. Because of this, and in the absence of a more prolonged sequential study of individual members of the population, it is not possible to conclude that the titre increases with advancing years. In the single rural (Wensleydale) sample in which all age groups over 15 years were examined, the prevalence of sero-positive subjects was lower in males than females, mainly because no males aged over 54 years were sero-positive in this particular rural sample.

In both Leigh and Wensleydale, the distribution of titres followed a simple curve in males and females. Moreover, in the Leigh sample, in which there was a greater prevalence of positive S.C.A.T. results, the titre curve was set at a higher level in both the negative and positive titre ranges. These findings suggest that the factor measured by the test may be a continuous variable and that differences in titre mainly reflect differences in degree of activity of the same serum factor. If so, this factor appears to be present in greater or lesser degree in 17 to 40 per cent. of the adult population. Absence of agglutination with the present method does not, however, signify absence of agglutinating factor because of the relatively low sensitivity of the test procedure. By increasing the concentration of amboceptor we have, in fact, been able to induce agglutinating activity in an appreciable proportion of sera with a titre of less than 4 in the present method. It has been argued on theoretical grounds that agglutination in low serum dilutions may be due to non-specific factors (Vaughan, 1959); and Heller, Jacobson, and Kolodny (1949) claimed that the titre of most rheumatoid sera was enhanced by sheep serum, but that the titre of (weakly reacting) non-rheumatoid sera was not. It seemed important, therefore, to find out the effect of sheep serum on sera having various titres in the S.C.A.T. When the saline diluent in our test procedure was replaced by 1 to 5 per cent. sheep serum in saline, 52 per cent. of 25 sera having titres in saline of 4 to 16 showed at least a 4-fold enhancement of titre as compared

with 67 per cent. of 36 sera with titres in saline of 32 to 1,024 (unpublished observations). Thus, in terms of their susceptibility to titre enhancement by sheep serum, no sharp distinction can be drawn between sera which in our test procedure have titres of 4 to 16 and those with higher titres. This result supports the conclusions derived from a consideration of the titre distribution curve.

Only about 20 per cent. of 93 sero-positive individuals in a large population sample presented clinical or radiological evidence of rheumatoid arthritis. It would seem, therefore, that there are more healthy individuals with a positive test than rheumatoid arthritics. Nevertheless, the prevalence of rheumatoid arthritis rose sharply, as expected, in the titre groups above 16.

Two of seven sero-positive non-rheumatoid subjects in the Leigh random sample were found to have developed rheumatoid arthritis when examined 5 years later. Significant serological titres may thus antedate clinical evidence of rheumatoid disease. Among nine rheumatoid arthritics included in the five-year follow-up, out of five initially sero-positive subjects one had deteriorated, and out of the four initially classified as sero-negative, two were found to have gone into remission. Sero-positive individuals may thus be more prone to develop rheumatoid arthritis, and sero-positive arthritics may fare worse than sero-negative arthritics, but a much larger series must be studied to prove this. The present findings are, however, in accord with those of Kellgren (1957) and Duthie, Brown, Knox, and Thompson (1957), who have presented evidence for the relatively poor prognosis of sero-positive rheumatoid disease.

Summary

(1) The titre of the rheumatoid serum factor detected by sheep cells sensitized by rabbit haemolysin was determined in subjects aged 55 to 64 years in seven European population samples. Positive titres occurred in 1·6 to 5·4 per cent. of the subjects tested. The prevalence of positive tests was significantly greater in urban than rural populations. In these urban and rural samples, the proportion of positive reactors was similar in males and females.

(2) In an urban sample including all age groups over 15 years, positive tests were also equally distributed among males and females; but in the single rural sample with this age range positive tests occurred more frequently in females than in males.

(3) The prevalence of positive tests increased with age in two urban samples; a similar result was obtained among females, but not among males, in the single rural sample.

(4) The titre distribution curve in rural and urban populations suggests that the serum factor is a continuous variable present in some degree in 17 to 40 per cent. of adults and possibly more.

(5) The titre was determined in the first-degree relatives of 261 members of an urban population sample. Positive titres occurred in 3 per cent. of relatives of propositi with a titre of up to 4, and in 12 per cent. of relatives of propositi with a titre of 128 and more. Since positive tests in both husband and wife were not found more frequently than would be expected by chance, it was concluded that genetic rather than environmental factors were responsible for the observed familial aggregation of positive titres.

(6) Only about 20 per cent. of sero-positive individuals in random samples presented evidence of rheumatoid arthritis as defined by the criteria of the American Rheumatism Association.

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REFERENCES

Abruzzo, J. L., and Christian, C. L. (1961). *Arthr. and Rheum.*, **4**, 103.
Ball, J. (1950). *Lancet*, **2**, 520.
Bremner, J. M., Alexander, W. R. M., and Duthie, J. J. R. (1959). *Ann. rheum. Dis.*, **18**, 279.
Cochran, J. B., Clayson, C., and Fletcher, W. B. (1957). *Brit. med. J.*, **2**, 185.
Dixon, A. St. J. (1960). *Ann. rheum. Dis.*, **19**, 209.
Duthie, J. J. R., Brown, P. E., Knox, J. D. E., and Thompson, M. (1957). *Ibid.*, **16**, 411.
Goldenberg, A., Singer, J. M., and Plotz, C. M. (1960). Annual Meeting of American Rheumatism Association, June, 1960, p. 39.
Heller, G., Jacobson, A. S., and Kolodny, M. H. (1949). *Proc. Soc. exp. Biol. (N.Y.)*, **72**, 316.
Kellgren, J. H. (1957). *Brit. med. J.*, **1**, 850.
—— and Ball, J. (1959). *Ibid.*, **1**, 523.
—— and Lawrence, J. S. (1956). *Ann. rheum. Dis.*, **15**, 1.
Kunkel, H. G., Simon, H. J., and Fudenberg, H. (1958). *Arthr. and Rheum.*, **1**, 289.
Lawrence, J. S., and Ball, J. (1958). *Ann. rheum. Dis.*, **17**, 160.
—— and Bennett, P. H. (1960). *Ibid.*, **19**, 20.
Lerner, E. M., Bloch, K. J., and Williams, R. R. (1960). *Arthr. and Rheum.*, **3**, 26.
Peltier, A., and Christian, C. L. (1959). *Ibid.*, **2**, 1.
Robecchi, A., and Daneo, V. (1959). *Acta rheum. scand.*, **5**, 245.

Ropes, M., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1959). *Ann. rheum. Dis.*, **18**, 49.
Vaughan, J. H. (1959). *Amer. J. Med.*, **26**, 596.
—— and Good, R. A. (1958). *Arthr. and Rheum.*, **1**, 99.
Ziff, M., Schmid, F. R., Lewis, A. J., and Tanner, M. (1958). *Ibid.*, **1**, 392.

Epidémiologie de la réaction d'agglutination des globules de mouton

RÉSUMÉ

(1) On détermina le titre du facteur rhumatismal sérique révélé par l'agglutination des globules rouges de mouton par l'hémolysine de lapin dans sept échantillons de la population européenne, chez des sujets âgés entre 55 et 64 ans. On obtint des titres positifs chez 1,6 à 5,4 pour cent des sujets examinés. Le pourcentage des reactions positives fut appréciablement supérieur parmi les populations urbaines que parmi les rurales. Dans les deux types de population la proportion des résultats positifs chez des hommes et des femmes fut similaire.

(2) Dans un échantillon de population urbaine comprenant tous les âges au dessus de 15 ans, les résultats positifs furent repartis également entre les deux sexes, mais dans un échantillon unique de population rurale avec une échelle d'âges similaire, les réactions positives furent plus fréquentes parmi les femmes.

(3) On nota une augmentation du nombre des réactions positives avec l'âge dans deux échantillons de population urbaine; un résultat similaire fut obtenu parmi les femmes, mais non pas parmi les hommes, dans le seul échantillon de population rurale.

(4) La courbe de distribution des titres dans des populations rurales et urbaines indique que le facteur sérique est une variable continue présente à un certain degré en 17 à 40 pour cent de la population adulte et, peut-être, plus que ça.

(5) On détermina le titre d'agglutination chez de proches parents de 261 membres d'un échantillon de population urbaine. Ces titres furent positifs en 3 pour cent des parents des sujets avec un titre de 4 et en 12 pour cent des parents des sujets avec un titre de 128 ou plus. Puisque des réactions positives chez les deux époux ne furent pas trop fréquentes, on conclut que l'agrégation familiale des titres positifs est due plus aux facteurs génétiques qu'ambiants.

(6) Seulement 20 pour cent à peu près des sujets séropositifs trouvés dans des échantillons pris au hasard présentait un tableau d'arthrite rhumatismale définie par les critères de la *American Rheumatism Association.*

Epidemiología de la reacción de aglutinación de los eritrocitos de carnero

SUMARIO

(1) Se determinó et título del factor reumatoide sérico revelado por la aglutinación de los eritrocitos de carnero sensibilizados con hemolisina de conejo en siete muestras de poblacion de Europa, en indivíduos de edades comprendidas entre 55 y 64 años. Aparecieron títulos positivos en el 1,6 a 5,4 por ciento de los sujetos examinados. El porcentaje de reacciones positivas fué significativamente superior entre las poblaciones urbanas que entre las rurales. En ambos tipos de población la proporción de positividades en hombres y mujeres fué similar.

(2) En una muestra de población urbana incluyendo todas las edades por encima de 15 años, los resultados positivos estuvieron repartidos por igual entre ambos sexos, pero en una sola muestra de población rural, con una escala de edades similar, las reacciones positivas fueron más frecuentes entre las mujeres.

(3) Se apreció un incremento de número de reacciones positivas con el aumento de edad en dos muestras de población urbana; un resultado similar se obtuvo entre las mujeres, pero no entre los hombres, en una sola muestra de población rural.

(4) La curva de distribución de los títulos en poblaciones rurales y urbanas sugiere que el factor sérico es una variable continua presente en cierto grado entre el 17 al 40 por ciento de la población adulta y posiblemente más.

(5) Se determinó el título de aglutinación en los los familiares de primer grado de 261 miembros de una muestra de población urbana. Entre los familiares de sujetos con un título de aglutinación de hasta 4 se encontró un 3 por ciento de títulos positivos, y un 12 por ciento entre los familaires de aquellos indivíduos con títulos de 128 y más. Como reacciones positivas en ambos cónyuges no aparecieron con una frecuencia superior a la que es de esperar por factores de azar, se concluyó que la agregación familiar de títulos positivos observada era debida más a factores genéticos que a ambientales.

(6) Solamente alrededor del 20 por ciento de los individuos seropositivos encontrados en muestras tomadas al azar, presentaban el cuadro de artritis reumatoide, aplicando el criterio de la *American Rheumatism Association.*

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PITUITARY CORTICOTROPHIN (ACTH) PRODUCTION IN RHEUMATOID ARTHRITIS TESTED INDIRECTLY WITH METOPIRON (Su 4885)

BY

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Metopiron [2-methyl-1,2-bis-3-pyridyl)-1-propanone; Su 4885] inhibits 11-β-hydroxylation in the adrenal cortex, and this inhibition is reflected as an increased production of ACTH in the anterior pituitary. It was found by Liddle, Estep, Kendall, Williams, and Townes (1959) that the pituitary production of ACTH in man can be measured with aid of Metopiron and numerous clinical studies have since been carried out which have shown that the Metopiron test can be employed as a reliable indirect method of evaluating the pituitary production of ACTH (*e.g.* Andersson, 1961; Faber, 1961; Gold, Kent, and Forsham, 1961).

In this paper we report results that obtained when the Metopiron test was applied to patients with rheumatoid arthritis.

Material and Methods

Our rheumatoid group comprised ten patients (3 male, 7 female; average age 53·7 yrs) who had not received steroid treatment for one year before the experiment.

The control group also comprised ten patients (3 male, 7 female; average age 46·0 yrs); the diagnoses of these patients are shown in Table II.

The patients in both groups were hospitalized during the whole experimental period of 6 days. The first, second, fifth, and sixth days were control days when Metopiron was not administered. On the third and fourth days the patients were all given 500 mg. Metopiron orally every 6 hours.

The 24-hr urine was collected and analysed for total 17-hydroxycorticosteroids (17-OHCS) by a modification of the method of Jenkins, Forsham, Laidlaw, Reddy, and Thorn (1955).

Results

The results of the Metopiron tests for the rheumatoid and control groups are summarized in Tables I and II (opposite).

The differences between the mean values for the two groups are not statistically significant. A tendency for a delayed reaction in the Metopiron test was evident in the rheumatoid group. The maximal average excretion of total 17-OHCS was recorded in the rheumatoid group on the fifth day (the day following the Metopiron administration), whereas it was recorded on the fourth day (the second day of Metopiron administration) in the control group.

Discussion

Our results seem to indicate that in rheumatoid patients the capacity of the pituitary to produce ACTH, as determined indirectly by the exogenous inhibition of 11-β-hydroxylation in the adrenal cortex, does not differ from the capacity in patients with various "non-collagenous" diseases. A tendency was noted in the rheumatoid patients for the response of the pituitary to be delayed, but it was not possible to determine on the basis of our results whether this finding was accidental or not. In an earlier study (Kalliomäki and Rauramo, 1960), it was found that urinary excretion of gonadotrophins is normal in female rheumatoid patients. Signs suggesting the thyrohypophyseal syndrome and an increased extracellular phase in rheumatoid arthritis (Kalliomäki and Holopainen, 1956; Kalliomäki, Kirpilä, Koskinen, and Laine, 1958) may reflect disturbances in the hypothalamo-pituitary system. It is possible that the delayed response of the anterior pituitary gland in the Metopiron test is also a manifestation of the same kind.

Metopiron has weak diuretic properties (it inhibits aldosterone production). Tables I and II show that the average total output of urine of the rheumatoid patients on the third, fourth, and fifth days was about half a litre larger than the average output in the control group. This may be taken as an indication of the above-mentioned predisposition to an increase in the extracellular fluid

TABLE I

RESULTS OF METOPIRON TEST IN THE RHEUMATOID GROUP

Case No.	Sex	Age (yrs)	History of Rheumatoid Arthritis (yrs)	Stage of Rheumatoid Arthritis	Erythrocyte Sedimentation Rate (mm./hr)	Urinary Excretion of Total 17-OHCS (mg./24 hrs)					
						Days					
						Control		Metopiron		Control	
						1	2	3	4	5	6
1	M	44	30	III	100	19·2	12·6	12·8	6·8	16·0	9·8
2	M	33	5	III	60	1·8	3·4	9·1	5·8	2·6	3·4
3	M	52	27	III	84	2·0	6·2	5·4	6·5	2·4	3·7
4	F	38	1/4	II	117	5·9	2·1	8·4	9·2	13·9	2·0
5	F	63	1/3	II	74	8·4	5·6	9·5	12·0	7·6	3·7
6	F	69	8	III	43	2·5	2·9	9·2	6·4	8·4	2·4
7	F	55	8	IV	31	11·0	4·6	11·2	18·6	12·9	8·0
8	F	67	30	IV	50	4·8	1·3	8·8	5·8	11·8	6·9
9	F	19	10	IV	20	4·5	2·3	10·3	13·9	13·0	1·7
10	F	50	17	III	54	3·1	2·3	4·3	4·1	4·9	7·0
Mean Total 17-OHCS Excreted (mg./24 hrs)						6·3	4·3	8·9	8·9	9·4	4·9
Average Volume 24-hrs Urine (ml.)						1,080	990	1,415	1,105	1,210	925

TABLE II

RESULTS OF METOPIRON TEST IN THE CONTROL GROUP

Case No.	Sex	Age (yrs)	Diagnosis	Urinary Excretion of Total 17-OHCS (mg./24 hrs)					
				Days					
				Control		Metopiron		Control	
				1	2	3	4	5	6
1	M	64	Cardiac infarction	4·3	4·0	12·2	10·5	5·2	lacking
2	M	56	Cardiac infarction	3·2	1·8	2·1	1·4	0·8	lacking
3	M	43	Cardiac infarction	4·0	6·0	5·2	8·4	8·4	2·1
4	F	54	"Little stroke"	13·5	5·9	13·2	19·7	13·5	4·5
5	F	62	Peptic ulcer	7·2	7·2	8·1	6·9	6·7	4·6
6	F	52	Angina pectoris	3·4	1·4	4·4	7·2	3·2	1·4
7	F	47	Acute infection	8·2	5·8	8·6	7·2	5·6	5·4
8	F	34	Hypochromic anaemia	6·0	4·3	4·2	9·7	3·8	lacking
9	F	66	Pleural carcinosis	12·0	13·9	17·3	14·0	20·0	10·0
10	F	59	Hodgkin's disease	4·1	5·0	9·2	13·6	13·8	10·4
Mean Total 17-OHCS Excreted (mg./24 hrs)				6·6	5·5	8·5	9·9	8·1	5·5
Average Volume 24-hrs Urine (ml.)				1,185	840	1,238	1,095	1,000]	920

phase and to increased oedema in rheumatoid arthritis.

Summary

The variation of the production of ACTH by the pituitary gland when 11-β-hydroxylation in the adrenal cortex is inhibited by Metopiron ("Su4885") has been followed by determining the mean daily excretion of total 17-hydroxycorticosteroids in ten patients with rheumatoid arthritis and in ten control patients with various internal diseases.

The response of the pituitary gland did not differ essentially in the rheumatoid and control groups, although a tendency for the response to be delayed was noted in the patients with rheumatoid arthritis.

REFERENCES

Andersson, E. (1961). *Ugeskr. Laeg.*, **123**, 223.
Faber, V. (1961). *Ibid.*, **123**, 227.
Gold, E. M., Kent, J. R., and Forsham, P. H. (1961). *Ann. intern. Med.*, **54**, 175.
Jenkins, D., Forsham, P. H., Laidlaw, J. C., Reddy, W. J., and Thorn, G. W. (1955). *Amer. J. Med.*, **18**, 3.
Kalliomäki, J. L., and Holopainen, T. E. (1956). *Acta rheum. scand.*, **2**, 213.
——, Kirpilä, J., Koskinen, H.-M., and Laine, V. A. I. (1958). *Ibid.*, **4**, 79.
—— and Rauramo, L. (1960). *Acta endocrinol.* (*Kbh.*), **34**, 45.
Liddle, G. W., Estep, H. L., Kendall, J. W., Williams, W. C., and Townes, A. W. (1959). *J. clin. Endocrinol.*, **19**, 875.

Production de corticotrophine (ACTH) dans l'arthrite rhumatismale sous l'influence indirecte de Metopiron (Su 4885)

RÉSUMÉ

On étudia les variations dans la formation d'ACTH par l'hypophyse après l'inhibition de l'hydroxylation en position 11-B dans l'écorce surrénale par Metopiron (Su 4885), en déterminant l'élimination moyenne totale par jour des 17-hydroxycorticostéroïdes chez dix malades atteints d'arthrite rhumatismale et dix témoins souffrant de diverses autres maladies.

La réponse hypophysaire ne révéla pas de différence essentielle entre le groupe rhumatismal et le groupe témoin, mas chez les malades atteints d'arthrite rhumatismale on nota une tendence à répondre tardivement.

Producción de corticotrofina hipofisaria (ACTH) suscitada indirectamente en artritis reumatoide con Metopiron (Su 4885)

SUMARIO

Se estudiaron las variaciones en la producción de ACTH por la hipófisis, después de inhibir la 11-B-hidroxilación en la corteza suprarrenal con Metopiron (Su 4665), determinando la eliminación media diaria de 17-hidroxocorticosteroides en diez enfermos con artritis reumatoide y en diez testigos padeciendo de diversas otras enfermedades.

La respuesta hipofisaria no presentó ninguna diferencia esencial entre el grupo con artritis reumatoide y el de control, aunque en los enfermos con artritis reumatoide se notó tendencia a respuestas retardadas.

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SACRO-ILIAC JOINT IN ADULT RHEUMATOID ARTHRITIS AND PSORIATIC ARTHROPATHY*

BY

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Sacro-iliitis is held to be an early and constant sign of ankylosing spondylitis (AS), a frequent sign of Reiter's disease, and one by which it is possible to distinguish these diseases radiologically from rheumatoid arthritis (RA).

Recently Cohen, McNeil, Sharp, Schubart, Calabro, and Calkins (1959), in a combined clinical and radiological study of AS and RA, briefly noted that "the sacro-iliac joints were involved in fifteen (27 per cent.) of 55 patients judged clinically to have only peripheral joint disease", a finding which might impair the validity of sacro-iliitis as a differentiating sign and might suggest that the two diseases, RA and AS, were part of the same pathological process.

The radiographic appearance of the normal sacro-iliac joint varies from individual to individual, and with age, sex, radiological technique, and the density of soft tissue shadows. These variable factors open the possibility of error in diagnosis. We felt that the only satisfactory method of determining the true incidence of radiological sacro-iliitis in RA would be that of the controlled study.

* Read at a meeting of the Heberden Society on December 3, 1960.

Material

297 radiographs of the sacro-iliac joints (Table I). These were selected as follows:

56 films were from adult patients with "classical" rheumatoid arthritis (Ropes, Bennett, Cobb, Jacox, and Jessar, 1959), in whom a modification of the differential agglutination test (D.A.T.) (Scott, 1952) was positive. These patients had all been under the care of Prof. E. G. L. Bywaters or one of us (A.S.D.), and the great majority had been personally studied as in-patients.

56 control films from patients matched for age and sex were taken from the files of the Radiology Department of patients with miscellaneous non-rheumatic conditions.

40 films from similarly studied adult patients with "definite" and "probable" rheumatoid arthritis (American Rheumatism Association Criteria), but with a negative D.A.T., with 40 matched control films.

33 films from patients with psoriasis and chronic inflammatory polyarthritis, with 33 matched control films. The patients in this group have been separately described (Lience, 1960).

36 films from patients with ankylosing spondylitis, found by reference to our files. These patients were either seen personally or were amongst

TABLE I

AGE AND SEX OF PATIENTS STUDIED

Films Studied	No. of Patients			Mean Age (yrs		Age Range (yrs)		Comment
	Total	Male	Female	Male	Female	Male	Female	
"Classical" Rheumatoid Arthritis ..	56	23	33	54	52	22–73	20–73	American Rheumatism Association Criteria: "Classical"
Matched Controls	56	23	33	54	52	22–72	20–70	
Sero-Negative Rheumatoid Arthritis	40	13	27	45	59	25–75	20–70	American Rheumatism Association Criteria: "Definite" "Probable"
Matched Controls	40	13	27	43	60	25–75	22–70	
Psoriasis and Arthritis	33	13	20	46	52	29–62	13–75	
Matched Controls	33	13	20	46	52	29–62	13–77	Controls without psoriasis and without arthritis
Ankylosing Spondylitis	36	31	5	43	40	21–73	33–47	Positive controls

those previously reviewed from this centre (Wilkinson and Bywaters, 1958).

Antero-posterior radiographs of the pelvis or lumbar spine are taken routinely on in-patients, but only when clinically indicated on out-patients—for example, by possible hip pain. Thus the study is weighted in favour of arthritis with more severe disease and hip involvement. A film was selected from the file of each patient or control according to the following order of preference:

(1) antero-posterior projection of whole pelvis;
(2) antero-posterior projection of both sacro-iliac joints;
(3) antero-posterior projection of lower lumbar spine, including sacro-iliac joints;
(4) antero-posterior projection of pelvis, as in views of the bladder before excretion urography.

Each type of projection was represented in each disease or control group, but there were slightly more projections of types (3) and (4) amongst the controls. We did not find that this interfered with reading the films when in random order.

Two films, one in the D.A.T.-positive and one in the D.A.T.-negative R.A. series, were rejected because Paget's disease of the pelvis made reading of the sacro-iliac joints unreliable. Their paired control films were similarly rejected.

Reading of Films

Each film was masked to exclude identifying marks and hips so as to reveal a rectangle containing both the sacro-iliac joints and the space between. The films were then shuffled, numbered, and arranged in random order, and read by both authors, jointly, and at a single sitting. The whole procedure was repeated at second and third readings. The first reading was regarded as a "practice run", and the results of the second and third readings were used for evaluation of repeatability and diagnosis.

Each sacro-iliac joint was thus read three times for each of the following characteristics: erosions, sclerosis, narrowing, and widening. Each characteristic was graded 0-3 (indicating no change, doubtful, definite, or severe change respectively). Grade 3 narrowing indicated fusion of the joint. When one part of a joint seemed wide and another narrow the overall impression was recorded. Fused joints cannot be graded for erosions and sclerosis, and films showing fusion of either joint were excluded from further analysis. Porosis of the bones forming the joint is another sign of sacro-iliitis, but one which we were unable to judge reliably because of the variation in density of the films. Attention was mainly directed to the synovial joint, which occupies the lower one-half to two-thirds of the apparent joint space according to the view. (The upper part of the joint is a synostosis.) Help was also obtained by reference to the disarticulated skeleton and to the anatomical and radiographical studies of the normal sacro-iliac joint of Forestier, Rotés-Querol, and Jacqueline (1950). Observations were also made on the ligamentous ossification where this was visible within the rectangle revealed by the masking.

Results

Repeatability (Table II).—Grading could be repeated with a satisfactory precision of about 84 per cent. and changes of two or three grades on repetition were not seen with erosions or sclerosis and were rare for widening or narrowing. Of more clinical significance is the repeatability of the diagnosis of definite abnormality. In the second column are listed the percentage scored for Grade 1 or 0 on both readings (*i.e.* pathology absent or doubtful). This corresponds to the normal cutting line of clinical diagnosis and at this level only 4 per cent. or less of all films have been allotted on one occasion to a normal or probably normal category and on another occasion to an abnormal category.

TABLE II
REPEATABILITY OF GRADING (per cent.)

Criterion	No Variation in Grade between 2nd and 3rd readings	No Change across the Line between Grade 1 and Grade 2
Narrowing ..	84	96
Erosions ..	85	98
Sclerosis ..	86	97
Widening ..	84	96

These figures must also be related to the total diagnoses of abnormality as well as to the total number of films studied. Thus consistency was shown three times as often as inconsistency in the selection of definite erosions, and two and a half times as often as inconsistency in the selection of definite narrowing, but as many films were read inconsistently as consistently for the presence of Grade II or more sclerosis. Definite "widening" of the joint was difficult to judge, since it was read inconsistently about twice as frequently as consistently and has therefore not been further analysed.

"Classical" RA (Table III).—Only 74 out of 112 joints of patients with "classical" RA were consistently diagnosed as Grade 0 (*i.e.* no narrowing), compared with 106 out of 112 joints of controls. The difference is significant ($P = <0{\cdot}01$), and at each level of grading more RA films were thought to show narrowing.

TABLE III

56 FILMS FROM PATIENTS WITH "CLASSICAL" RHEUMATOID ARTHRITIS AND 56 CONTROLS

Subjects	All Films		Films showing Fusion are Excluded	
	Narrowing		*Erosions*	*Sclerosis*
56 Cases of "Classical" Rheumatoid Arthritis	74 4 / 14 9 2 / 3 2 2 / 1 1		83 4 / 8 10 1 / 2	91 4 / 7 5 / 1
56 Controls	104 1 / 5 2		82 11 / 7 10 2	93 4 / 6 6 2 / 1

Note: In this and in Tables IV to VI, the numerals refer to the number of sacro-iliac joints. The grading for the second reading is given by the vertical scale, and for the third reading by the horizontal scale.

Thus consistent gradings will be found in heavy type in the central diagonal from bottom left to top right.

Two films graded as having a fused joint or joints at either reading have been omitted from the analysis of erosions and sclerosis, which shows that there is no difference in grading between the cases of classical rheumatoid arthritis and the controls for these features.

Radiological diagnosis is, in practice, a matter of assessing the total picture rather than of grading individual features. The great majority of the RA sacro-iliac joints could not be distinguished from those of the controls, but in one or two cases we did think it might be possible to recognize a "rheumatoid" sacro-iliac joint change, which occurs in older people and consists of narrowing, with small, ill-defined erosions and general osteoporosis without ligamentous ossification (as seen in the left sacro-iliac joint in Fig. 1 (overleaf), which was graded as showing doubtful erosions, sclerosis, and narrowing at both readings). The right sacro-iliac joint in the same subject had been graded as normal for all criteria at both readings.

To investigate this point further, the gradings of various criteria were related to the age of the patient (Fig. 2), which showed that narrowing of the sacro-iliac joint was much commoner in D.A.T.-positive

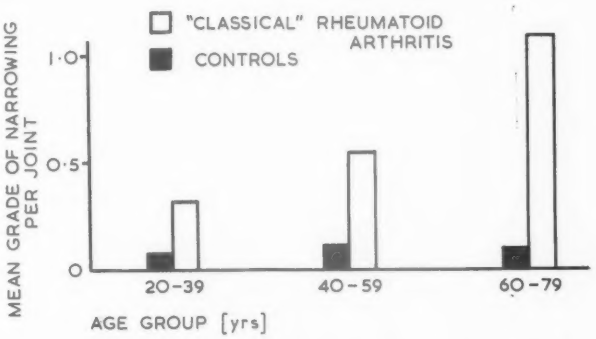


Fig. 2.—For each 20-year age group the total score for narrowing of both sacro-iliac joints has been summed up and divided by the number of films.

RA patients than in their controls at all ages. Moreover, the scores for narrowing increased with age and thus probably with duration of disease, whilst the scores for narrowing amongst the controls were scarcely affected by age. One man (Fig. 3, overleaf) and one woman with RA were thought to have fused sacro-iliac joints. Both had severe RA of at least 20 and 25 years' duration respectively, and both also had very severe involvement (without

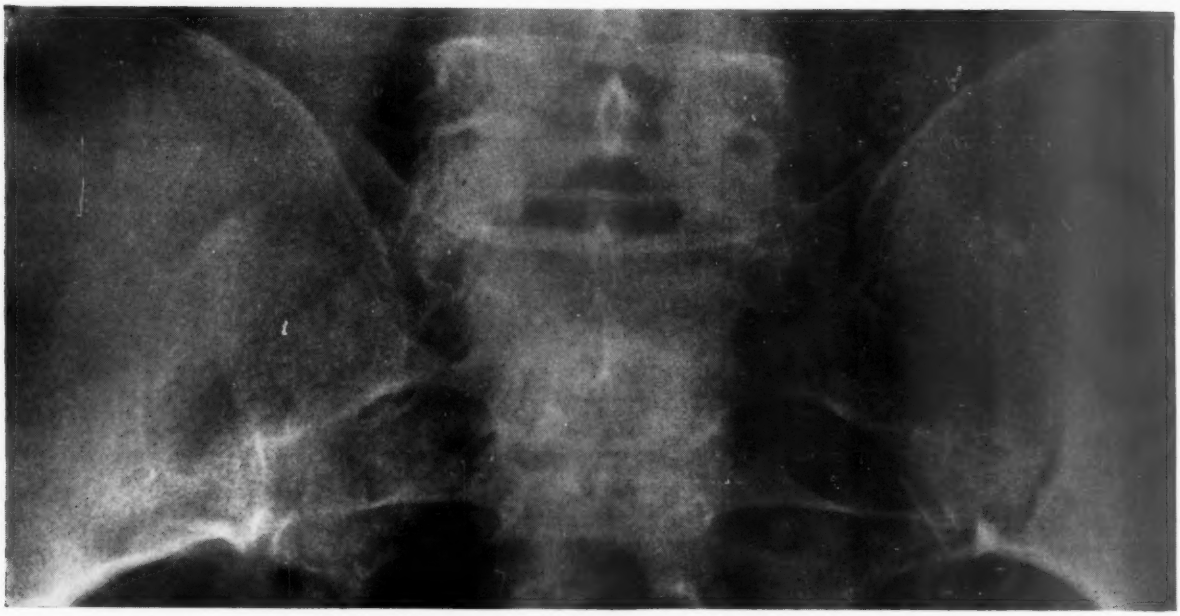


Fig. 1.—Grade 1 erosions, sclerosis, and narrowing in the left sacro- iliac joint of a patient with "classical" rheumatoid arthritis.

Fig. 3.—Fusion of sacro-iliac joints without ligamentous ossification in a man aged 64 with "classical" rheumatoid arthritis of 20 years' duration and severe hip involvement.

ankylosis) of the hips. Four patients with definite (Grade 2) narrowing also had some degree of clinical involvement of the hips. However, as there were also numerous patients with hip involvement, but without sacro-iliac narrowing, the association of hip involvement and sacro-iliac narrowing or fusion did not appear to be significant.

DAT-Negative RA.—Minor degrees of narrowing (Table IV) were diagnosed a little more frequently in the DAT-negative RA patients than in the controls, but the difference is not significant. A woman aged 73, a control, with Grade 3 narrowing (*i.e.* fused joints) at both readings (Fig. 4, overleaf), had no clinical or radiological evidence of spondylitis, but had been treated for a fractured femoral neck by a Smith-Peterson pin. There was no other explanation for her sacro-iliac fusion and she had no evidence of arthritis. She illustrates the fact that sacro-iliac fusion may occasionally occur without obvious cause. Narrowing did not appear to be related to age in this group.

No difference in erosions or sclerosis was found between patients and controls in this group.

Psoriasis and Arthritis (Table V, overleaf).—In the patients with psoriasis and arthritis there was a significant excess of sacro-iliac joints graded as showing definite narrowing or fusion. Four films showing fusion were withdrawn before consideration of other criteria.

A slight excess of patients was thought to have erosions, but difference is not striking. "Sclerosis" was the same for both patients and controls. We were unable to distinguish the films of those with fused joints from the appearances seen in ankylosing spondylitis.

Ankylosing Spondylitis.—A high proportion of patients with AS was considered to have definite narrowing or fusion of the sacro-iliac joints (Table VI, overleaf). Twenty films with fusion at one or other reading were withdrawn before consideration of other criteria.

TABLE IV

FORTY FILMS FROM PATIENTS WITH SERO-NEGATIVE RHEUMATOID ARTHRITIS AND FORTY CONTROLS

(Key as in Table III)

Subjects	All Films				Films showing Fusion are Excluded							
	Narrowing				*Erosions*				*Sclerosis*			
	3					3				3			
40 Cases of Sero-negative Rheumatoid Arthritis	2		1	1		2		1	1	2			
	1	6	3	3		1	4	5	1	1	3	10	1	
	0	58	8			0	62	6			0	65	1		
		0	1	2	3		0	1	2	3		0	1	2	3
	3				2	3					3				
40 Controls	2			1		2					2		1		
	1	2	2	1		1	6	3			1	5	1		
	0	66	6			0	64	5			0	68	3		
		0	1	2	3		0	1	2	3		0	1	2	3

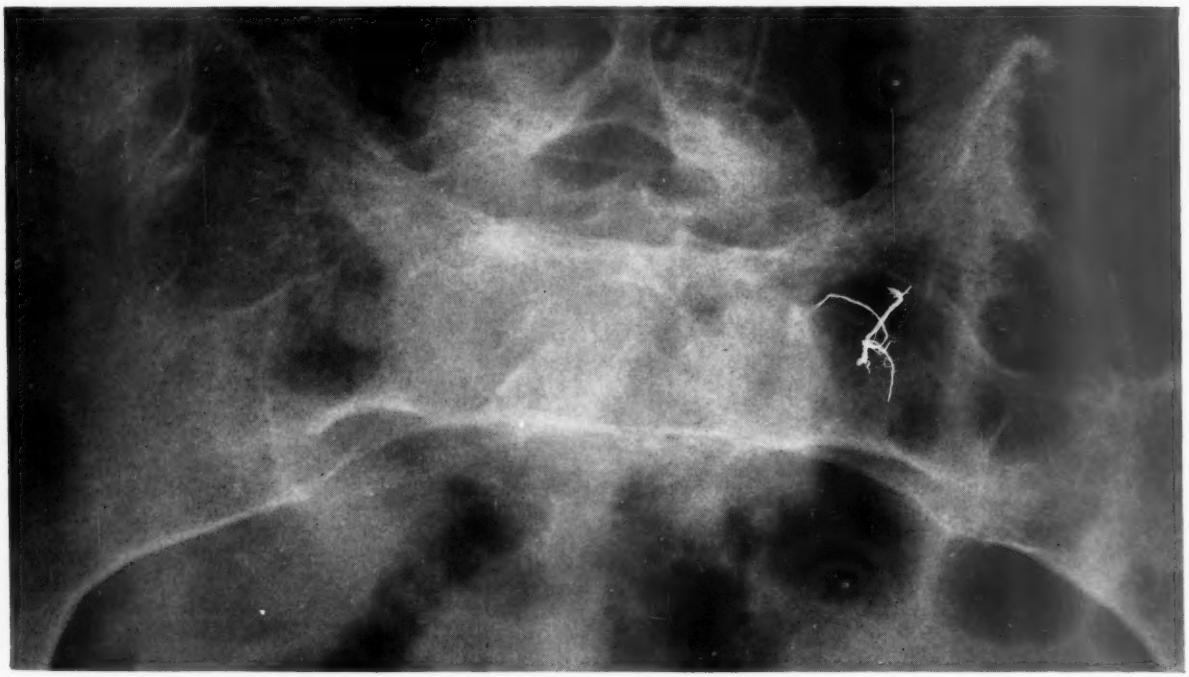


Fig. 4.—Fusion of sacro-iliac joints without ligamentous ossification in a woman aged 74, a control subject, without arthritis or spondylitis.

TABLE V

33 FILMS FROM PATIENTS WITH PSORIASIS AND ARTHRITIS AND 33 CONTROLS

(Key as in Table III)

Subjects	All Films — *Narrowing*				Films showing Fusion are Excluded — *Erosions*				— *Sclerosis*			
	3			1	6								
33 Cases of Psoriasis and Arthritis	2		2	4			3	1			1	1	
	1	2	3	3		4	8	1		2	7		
	0	43	2			38	3			41	6		
		0	1	2	3	0	1	2	3	0	1	2	3
	3												
33 Controls	2										1		
	1	4	3	1		5	1			10	3	1	
	0	57	1			57	3			50	1		
		0	1	2	3	0	1	2	3	0	1	2	3

TABLE VI

36 FILMS FROM PATIENTS WITH ANKYLOSING SPONDYLITIS

(Key as in Table III)

Subjects		*Narrowing*				*Erosions*				*Sclerosis*			
	3			2	37				13				6
36 Cases of Ankylosing Spondylitis	2		2	8	2			8	3		5	4	4
	1	2	2	2		1	2			3	2	3	
	0	9	2	4		2	1			1	2		
		0	1	2	3	0	1	2	3	0	1	2	3

Of the remainder, only three films were not consistently graded as "definite" (*i.e.* Grade 2 or more) for erosions or sclerosis. None was consistently thought to be normal (Grade 0), but in one case (Fig. 5) only doubtful (Grade 1) changes were recorded at both readings and was thus "missed". This was from a patient with pain down the back of one leg and a normal erythrocyte sedimentation rate, in whom the clinical diagnosis of AS was also doubtful.

Various other signs of AS were seen which did not occur in the other diagnostic group, except in four patients with psoriasis and spondylitis. These included in early cases gross "widening" of the joints (Fig. 6, overleaf), and in late cases "ghost joints", and also "stars"—radiating condensations of trabeculae at the upper end of the sacro-iliac joint (Hart and Robinson, 1959). In addition, the interspinous ligament of the sacrum was often ossified, in late cases producing an appearance rather like the shaft of

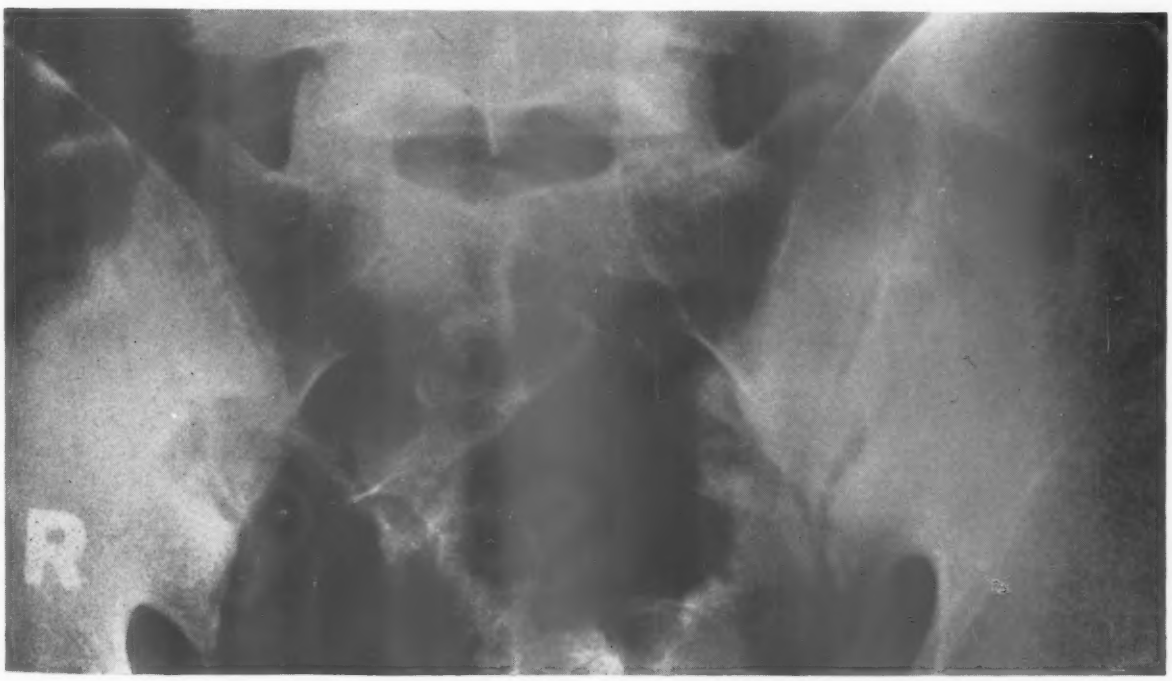


Fig. 5.—Changes in sacro-iliac joints doubtful. Clinical diagnosis of ankylosing spondylitis also doubtful.

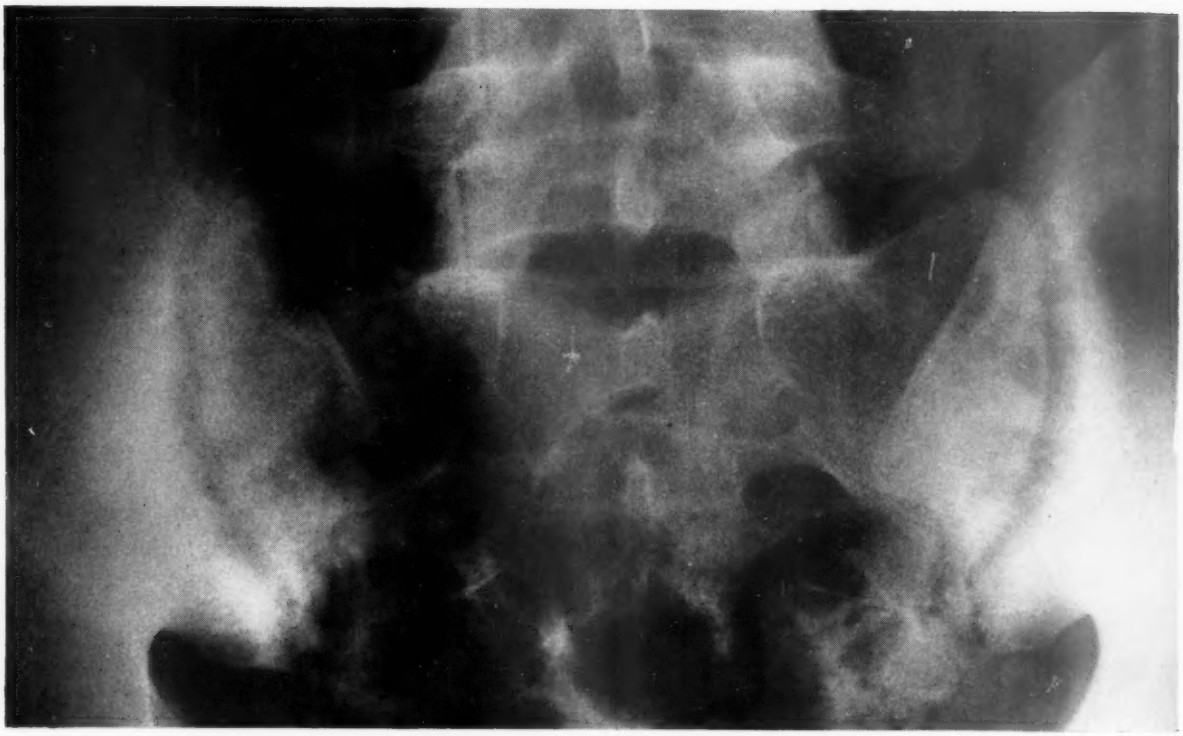


Fig. 6.—A case of ankylosing spondylitis showing gross widening. This appearance was not seen in the rheumatoid arthritis series.

a dagger, and the other ligaments, notably the iliolumbar, might also ossify (Fig. 7, opposite). "Stars", the "dagger sign", and gross widening of the joint did not occur in the control and rheumatoid films.

Normal Sacro-iliac Joints.—We also analysed our readings from the point of view of all gradings being normal (*i.e.* Grade 0 for narrowing, erosions, and sclerosis) and also as probably normal (*i.e.* Grade 1 or 0 for the same criteria). Results at the second and third reading were similar—those of the third reading are given in Table VII. As mentioned above, the film of one patient with AS was considered probably normal in these respects. For the other diagnostic groups there is a consistent trend for more films from control subjects than from patients to be considered free of definite abnormality, but this is significant only in the comparison of the psoriatic group with their controls.

TABLE VII

NUMBERS OF FILMS THOUGHT NORMAL FOR EROSIONS, SCLEROSIS, AND NARROWING

Series		No. of Subjects	All Grades Third Reading	
			0	0 or 1
D.A.T.-Positive	Rheumatoid Arthritis	56	31	51
	Controls	56	34	52
D.A.T.-Negative	Rheumatoid Arthritis	40	24	34
	Controls	40	28	37
Psoriasis and Arthritis		33	12	22
Controls		33	23	31
Ankylosing Spondylitis		36	0	1

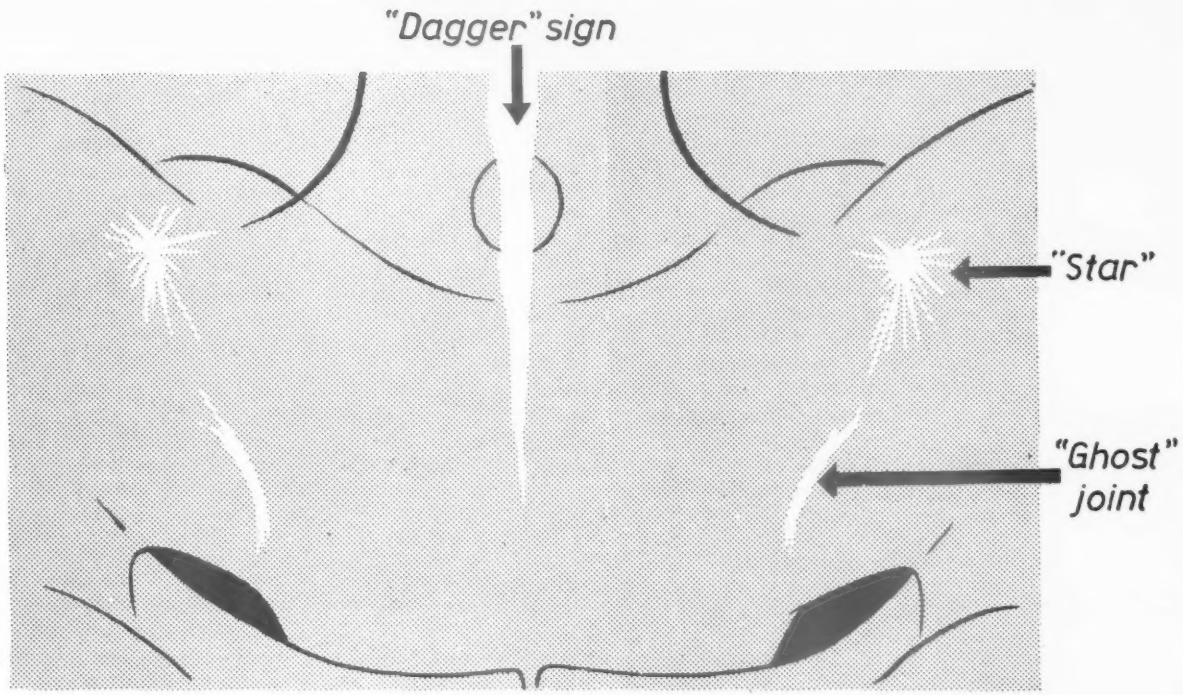
Figures in heavy type indicate significant differences.

Discussion

This study confirms that the sacro-iliac joints may occasionally be affected in rheumatoid arthritis, but that changes when they do occur consist of narrowing of the joint space with or without small, ill-defined erosions and without surrounding sclerosis. In this study these changes were found mainly in older patients with long-standing and severe disease. In no case did the appearances closely resemble those seen in the sacro-iliac joints in cases of ankylosing spondylitis.

The controls in this study also included a few patients with definite changes in the sacro-iliac joints. They represent the population of "hospital attenders", rather than the population as a whole. Through the courtesy of Dr. John Lawrence we

(*a*)



(*b*)

Fig. 7.—A case of late ankylosing spondylitis, showing the "ghost joints", "stars", and "dagger sign", which were not seen in the rheumatoid arthritis series.

were able to examine pelvic radiographs from a random sample of the normal population in the 55- to 64-year age group; 23 of these were technically comparable and it is of interest that minor degrees of sacro-iliac joint narrowing and the radiological appearance of Grade 1 erosions or sclerosis were occasionally encountered in this small group.

That the sacro-iliac joint does not escape involvement in generalized sero-positive rheumatoid arthritis is known from autopsy studies (Ball, 1957; Loewi, 1960). We feel, however, that the radiological evidence of this is late in appearance and different from that of ankylosing spondylitis. The validity of radiological examinations of the sacro-iliac joint in differentiating rheumatoid arthritis from ankylosing spondylitis is not impaired.

Summary

The radiological appearances of the sacro-iliac joints from 56 patients with D.A.T.-positive rheumatoid arthritis, forty with D.A.T.-negative rheumatoid arthritis, and 33 with psoriasis and chronic arthritis were compared with those of a control series comprising a similar number of hospital patients matched for age and sex, and also with those of 36 patients with ankylosing spondylitis. The films were read in random order. Repeatability of reading was satisfactory.

Narrowing of the sacro-iliac joints, without erosions or sclerosis, was found in older patients with long-standing rheumatoid arthritis. The appearances did not resemble those seen in early or late ankylosing spondylitis.

REFERENCES

Ball, J. (1957). Personal communication.

Cohen, A. S., McNeil, M., Sharp, J. T., Schubart, A., Calabro, J., and Calkins, E. (1959). Summarized in "Second Pan-American Congress on Rheumatic Diseases", p. 41.

Forestier, J., Rotés-Querol, J., and Jacqueline, F. (1950). *Rev. Rhum.*, **17**, 407.

Hart, F. Dudley, and Robinson, K. C. (1959). *Ann. rheum. Dis.*, **18**, 15.

Lience, E. (1960). M.D. Thesis, University of Barcelona.

Loewi, G. (1960). Personal communication.

Ropes, M. W., Bennett, G. A., Cobb, S., Jacox, R., and Jessar, R. A. (1959). *Ann. rheum. Dis.*, **18**, 49.

Scott, F. E. T. (1952). *Lancet*, **1**, 392.

Wilkinson, M., and Bywaters, E. G. L. (1958). *Ann. rheum. Dis.*, **17**, 209.

DISCUSSION

DR. V. WRIGHT (*Leeds*): We have been interested for some time in the clinical and radiological appearances of psoriatic arthritis and for that reason have routinely *x*-rayed the hands, feet, and sacro-iliac joints of all patients with psoriasis and rheumatic complaints. At the last analysis there were 157 patients, of whom 121 had psoriasis with erosive arthritis. Splitting this up, there were 103 with arthritis and a negative DAT, and eighteen with a positive test DAT. There were 99 sacro-iliac joints available for study in the psoriatic patients with negative DAT.

We then took 91 rheumatoid arthritics with a positive DAT and *x*-rayed the sacro-iliac joints. In the patients with psoriatic arthritis and a negative DAT there were erosions in nineteen, ankylosis in eight. In the rheumatoid group there were erosions in five and ankylosis in one (all unilateral). We took the group of patients with psoriatic arthritis and a positive DAT to have coincidental rheumatoid arthritis. The incidence of erosive changes in the sacro-iliac joints was the same as in the rheumatoid group, but in those who were considered to have psoriatic arthritis it was a good deal higher. Has Dr. Dixon any information on how his patients' *x* rays were related to the DAT?

DR. A. G. S. HILL (*Stoke Mandeville*): We have available 52 *x* rays of sacro-iliac joints of patients with psoriasis and locomotor disease. Nine had a positive DAT and none of these had sacro-iliac joint changes; 43 had a negative DAT, and ten of these had sclerosis or more advanced changes.

DR. J. FORESTIER (*Aix-les-Bains*): It is certain that one cannot draw any conclusions from the appearances of bony ankylosis in the sacro-iliac joints. The same sort of ankylosis is to be seen on *x*-ray films whatever the cause of the ankylosis. Also it is essential to remember that at the onset of ankylosing spondylitis there is no narrowing in the sacro-iliac joint. There is, as I described in 1937, a pseudo-enlargement, causing irregular dysfunction and loss of ossification on both sides of the joint line; it is only at a later stage that narrowing of the joints is seen in the form of bony streaks which appear from place to place.

Psoriatic arthritis is a debatable subject; I do not know whether there is such a condition as "rheumatoid spondylitis" or "psoriatic spondylosis", and it may be that "psoriatic arthritis" is an entity by itself.

DR. DIXON: Dr. Wright and Dr. Hill made substantially the same point. None of the patients with fusion and psoriatic arthropathy (or spondylosis) had a positive DAT, and I am afraid we did not have enough cases with a positive DAT to give you a meaningful breakdown.

I am very glad to have Dr. Forestier's comments. We referred to the excellent paper by himself, Rotés-Querol, and Jacqueline on the radiological and anatomical appearance of the sacro-iliac joint in normal adults in assessing our own patients.

I am a little worried about this question of a widening of the sacro-iliac joint occurring only in early ankylosing spondylitis, because of the difficulties in dating the onset of ankylosing spondylitis. The condition can only be dated from the onset of symptoms. I think that, if we say that all early cases first show widening, we must imagine that the apparently early cases without widening are in fact showing the results of a long era of silent arthritis.

Articulation sacroiliaque chez l'adulte atteint d'arthrite rhumatismale et d'arthropathie psoriasique

RÉSUMÉ

On compara les images radiologiques des articulations sacroiliaques de 56 malades atteints d'arthrite rhumatismale et ayant une réaction d'agglutination différentielle positive, de 40 malades avec arthrite rhumatismale et une réaction d'agglutination différentielle négative, et de 33 malades souffrant de psoriasis et d'arthrite chronique à celles obtenues chez un nombre égal de témoins hospitalisés, d'âge et sexe comparables, et aussi à des radiographies obtenues chez 36 malades atteints de spondylarthrite ankylosante. La lecture des radiographies se fit par hasard, sans aucun ordre. En

répétant les lectures on ne nota pas de divergence d'interprétation statistiquement appréciable.

Chez des malades d'un âge avancé, atteints d'une arthrite rhumatismale de longue durée on trouva un rétrécissement des articulations sacroiliaques, sans érosion ou sclérose. Les images ne ressemblèrent pas à celles observées dans la spondylarthrite ankylosante au début ou avancée.

La articulación sacroiliaca en adultos con artritis reumatoide y artropatia psoriásica

SUMARIO

Se compararon las imágenes radiológicas de las articulaciones sacroiliacas halladas en 56 enfermos con reacción de aglutinación diferencial positiva y artritis reumatoide, en 40 con esta reacción negativa y artritis reumatoide y en 33 con psoriasis y artritis crónica, con aquellas obtenidas en series de control comprendiendo un número similar de enfermos hospitalarios de edad y sexo comparables, y también con radiografías obtenidas en 36 enfermos con espondilartritis anquilosante. La lectura de las radiografías se realizó al azar, sin previo orden. Repetición de las lecturas no reveló divergencia estadísticamente apreciable.

En enfermos de edad avanzada, sufriendo de artritis reumatoide por largo tiempo se encontró estrechamiento de las articulaciones sacroiliacas, sin erosiones o esclerosis. Las imágenes no eran similares a las observadas en espondilartritis anquilosante incipiente o avanzada.

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TISSUE IRON AND THE RETICULO-ENDOTHELIAL SYSTEM IN RHEUMATOID ARTHRITIS

BY

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The cause of the normocytic hypochromic anaemia characteristic of rheumatoid arthritis remains unknown. Iron is absorbed normally from the gut (Roy, Alexander, and Duthie, 1955), but in an investigation of the iron content of the bone marrow (Richmond, Gardner, Roy, and Duthie, 1956) it was shown that stainable marrow iron was absent in nineteen of 61 cases and that there was no correlation between the presence or absence of iron in the marrow and the degree of anaemia.

It appeared likely that an unknown factor was interfering with the utilization of iron for the synthesis of haemoglobin. An increased tissue avidity for iron comparable to that postulated by Cartwright and Wintrobe (1952) as a cause of the anaemia of infection seemed a possible explanation. Earlier studies (Roy and others, 1955) had shown that saccharated oxide of iron injected intravenously was rapidly removed from the plasma of patients with rheumatoid arthritis. This observation supported the suggestion of the existence of a state of overactivity or of hyperplasia of the reticulo-endothelial system (Freireich, Ross, Bayles, Emerson, and Finch, 1957). Some evidence for such a hyperplasia was available from morphological studies (Sinclair and Cruickshank, 1956). Overactivity of the reticulo-endothelial system appeared to be a possible explanation for the paradox that iron found histologically in the bone marrow was not utilized in the synthesis of haemoglobin (Richmond and others, 1956).

On the basis of this hypothesis, it was postulated that in rheumatoid arthritis the organs comprising the reticulo-endothelial system might contain more iron than those of comparable subjects not suffering from this disease. The present investigation was planned to examine the validity of this hypothesis. The analysis was conducted in parallel by histological and biochemical methods. The bone marrow, although part of the reticulo-endothelial system, was not examined since it had been studied previously (Richmond and others, 1956).

Material

Samples of tissue from liver, spleen, lymph node, suprarenal, and lung were obtained from 34 patients with rheumatoid arthritis who died in hospital and from 43 patients not suffering from this disease.

Cases of Rheumatoid Arthritis (Tables I and II, opposite).—In fifteen cases there was evidence that the patient had not been given medicinal iron in any form. The organs of the reticulo-endothelial system of each were examined histologically, but in only seven were chemical analyses made. In the remaining eight cases, the available tissues were embedded in paraffin and extraction was found to interfere with the subsequent chemical estimation of iron.

Material was available from nineteen further patients to whom iron had been given by mouth, by intravenous or by intramuscular injection, or in the form of whole blood by transfusion. The tissues of eighteen were examined histologically and of seventeen chemically.

Cases without Rheumatoid Arthritis (Tables I and II).—Material was obtained from 43 patients. Chemical analyses were made on organs from each case, but in only 25 cases were all the organs examined histologically. This control material was divided into groups for comparison with the cases of rheumatoid arthritis.

Methods

Histological.—Tissue collected at necropsy was placed in clean glass containers with precautions to exclude contamination by environmental iron. Paraffin sections from this material were cut at 5-7μ. and stained for iron by a modification of the Prussian blue reaction (Richmond and others, 1956; Gardner, 1958). The

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TABLE I

TESTS CARRIED OUT IN CASES OF RHEUMATOID ARTHRITIS AND CONTROLS

Source of Material				Analysis	
				Histological	Chemical
34 Cases of Rheumatoid Arthritis	Total No. of Cases			33	24
	Males	Total		10	9
		Treated with Iron		5	6
		NOT treated with Iron		5	3
	Females	Total		23	15
		Treated with Iron		13	11
		NOT treated with Iron		10	4
	Mean Age (yrs)			58	60
	Range (yrs)			25–80	53–80
43 Control Cases	Total No. of Cases			25	43
	Group 1 (10) Sudden Death in Young Persons		Male	4	7
			Female	3	3
	Group 2 (16) Rapid Death in Older Persons		Male	4	8
			Female	5	8
	Group 3 (9) Comparable to Rheumatoid Arthritis Patients		Male	1	6
			Female	1	3
	Group 4 (8) Excess Storage Iron		Male	3	3
			Female	4	5

TABLE II

CAUSES OF DEATH IN CASES OF RHEUMATOID ARTHRITIS AND CONTROLS

Group		Causes of Death	Total Cases
Rheumatoid Arthritis	NOT Given Iron or Blood Transfusion	Carcinoma of colon, 3; chronic bronchitis, 2; primary carcinoma of liver, carcinoma of bronchus, leukaemia, meningitis, pneumonia, congestive cardiac failure, epilepsy, cervical dislocation, vena caval thrombosis, and anaesthesia, one each	15
	Given Iron or Blood Transfusion	Bronchopneumonia or purulent bronchitis, 3; amyloidosis, 3; carcinoma bronchus, carcinoma oesophagus, cor pulmonale, septicaemia, pyelonephritis, systemic candidiasis, hypertension, cardiac failure, cerebral infarction, aplastic anaemia, megaloblastic anaemia, gastric haemorrhage and steatorrhoea, and perforated stomal ulcer, one each	19
Controls	Group 1	Trauma, 6; anaesthesia, CO_2 poisoning, methanol poisoning, and subarachnoid haemorrhage, one each	10
	Group 2	Myocardial infarction, 5; cerebrovascular accident, 4; pulmonary embolism, 3; cor pulmonale, 2; malignant hypertension, and fractured femur, one each	16
	Group 3	Bronchopneumonia, 3; cerebral haemorrhage, intestinal obstruction, chronic cholecystitis, chronic duodenal ulcer, perforated peptic ulcer, and myocardial ischaemia, one each	9
	Group 4	Haemosiderosis, 5; polycythaemia, 2; injected intravenously with 1 g. iron immediately before death from cerebral vascular disease, 1	8

amount of iron in representative microscopic fields was assessed visually and graded by a simple notation ranging from nil (no iron seen) to 5 (large amount of iron seen).

Sections were also stained with haematoxylin and eosin, and in a number of instances frozen sections were examined by the Weil-Davenport silver impregnation technique described by Marshall (1956). With this material the morphological state of the reticulo-endothelial system was assessed. In the liver, the distribution of iron between hepatic and Kupffer cells was noted. Prominence of Kupffer cells and excessive numbers of mononuclear cells in the portal tracts were recorded. In the spleen and lymph nodes, lymphoid follicular hyperplasia, reticulum cell hyperplasia, erythrophagocytosis, and excess of plasma cells were tabulated. In the lung, lymphoid hyperplasia and excessive numbers of mononuclear cells were noted, and in the suprarenal the state of the phagocytic sinus cells was studied.

Chemical.—Material was collected at necropsy in clean jars and stored at −10° C. The method used for the chemical estimation of iron was essentially that of Ramsay and Campbell (1954). In a few instances fresh frozen tissue was not available and tissue which had been preserved in formalin for periods of up to 2 months was used (Kerr, 1957). Interference from haemoglobin was of significance only in tissues in which the concentration was very low. The method was shown to give a reasonable estimate of the non-haem iron concentration in all tissues with the exception of lung which was difficult to homogenize. Further difficulty was encountered where the lungs were those of city dwellers, on account of the presence of extraneous material of atmospheric origin.

Results

Morphological

I. Iron Content (Table III)

Rheumatoid Arthritis.—In patients not given iron therapeutically, the livers contained more iron than in control groups 1, 2, and 3, but less than in group 4. The spleens also had a slightly higher mean iron content, but the amount of iron seen in lymph nodes, lungs, or suprarenals was so slight that differences between the groups were not defined.

Iron was distributed in the reticulo-endothelial system of cases of untreated rheumatoid arthritis in the same manner as in the comparable control groups 2 and 3. Thus, in the spleen, iron was present as haemosiderin granules within the splenic pulp or sinusoids, or within macrophages lining the sinusoids. In twelve cases more was present within hepatic cells than within Kupffer cells.

The amount of iron found in the cases of rheumatoid arthritis treated with iron was greater than in those not so treated, in each of the organs examined. In five cases the Kupffer cells contained more iron than the hepatic cells. In patients who had been given iron by injection, iron was found in the phagocytic sinus cells and histiocytes of the lymph nodes. The iron content of the lung and suprarenal also conformed to this pattern, iron being present only in the phagocytic cells.

Control Groups.—The amount of iron found histologically varied considerably between the four groups. Iron was absent from the livers of cases in group 1, but was present in many of the livers of cases in groups 2 and 3, being seen as small granules scattered diffusely in the hepatic cells. Iron was present in the spleen in every case but tended to be present in greater amounts in the spleens of cases in groups 2 and 3 than in those of cases in group 1. It was most exceptional to find stainable iron in the lymph nodes, lungs, or suprarenals unless, as in group 4, there was some incidental clinical explanation for the local accumulation of iron-containing pigment.

II. Histology (Table IV, opposite)

The state of the cells in the five principal organs of the reticular system (Marshall, 1956) is recorded in Table IV. There was evidence of frequent portal round cell infiltration, of splenic and lymph-nodular follicular hyperplasia, and of an excessive number

Table III

TISSUE IRON CONTENT ASSESSED HISTOLOGICALLY AND CHEMICALLY
Histological Results: Arithmatic mean of arbitrary units
Chemical Results: mg. Fe/100 g. wet weight of tissue

Group			No. of Cases	Tissue				
				Liver	Spleen	Lymph Node	Lung	Suprarenal
Control	1	Total	10					
		Histological	7	0	0·55	0	0	0
		Chemical	10	11·1	11·5	1·5	2·5	3·3
	2	Total	16					
		Histological	10	0·25	0·56	0·4	0·2	0
		Chemical	16	16·9	22·2	2·9	5·5	3·5
	3	Total	9					
		Histological	2	0·1	0·8	0	0·1	0
		Chemical	9	17·2	32·1	3·3	5·4	3·5
	4	Total	8					
		Histological	6	2·3	3·0	2·0	0·5	0·5
		Chemical	8	238·1	97·6	67·4	6·2	4·2
Rheumatoid Arthritis	No Iron	Histological	15	0·5	1·0	0·4	0·2	0·2
		Chemical	7	20·0	21·8	4·7	3·6	3·3
	Iron	Histological	18	1·6	2·6	1·1	1·0	0·6
		Chemical	17	70·0	127·8	21·3	8·3	11·7

TABLE IV

HISTOLOGICAL EXAMINATION OF ORGANS OF RETICULO-ENDOTHELIAL SYSTEM IN CASES OF RHEUMATOID ARTHRITIS

Organ	No. Examined	Characteristic Recorded	Number in Which Found
Liver	34	Unusual prominence of Kupffer cells	1
		Excessive round cell foci	6
		Excess reticulum cells	4
		Abnormal number of round cells in portal tracts	18
Lymph Node	20	Follicular hyperplasia	7
		Sinus cell hyperplasia	9
		Excess reticulum cells	5
		Excess plasma cells	10
Spleen	34	Lymphoid follicular hyperplasia	5
		Erythrophagocytosis	0
		Excess reticulum cells / Excess sinus cells	3
		Excess plasma cells	7
Lungs	34	Lymphoid hyperplasia	7
		Excess reticulum cells	1
Suprarenal	25	Sinus cell hyperplasia	0

of splenic and lymph-nodular plasma cells. However, it was difficult to define quantitatively any histological feature which indicated hyperplasia or hyperactivity of reticulo-endothelial cells. It was equally clear that the obvious possibility that there had been a hyperplasia of reticulo-endothelial cells without an alteration in their concentration could not be excluded.

Chemical (Tables V, VI)

Rheumatoid Arthritis.—The mean iron concentration in the tissues from seven patients with rheumatoid arthritis to whom iron had not been given therapeutically did not differ significantly from those for the entire control series. The number of tissue analyses was too small to allow of any attempt at correlation between iron concentration and age and sex, but a tendency for values to increase with age, and to a higher level in males, was apparent.

Comparison with control groups 2 and 3 revealed an increase of iron concentration in the lymph nodes in rheumatoid arthritis. The iron content of the spleen was also significantly greater than that of the spleen in control group 1, but was not different from that of either group 2 or 3. The values for liver, lungs, and suprarenals from the rheumatoid cases did not differ from any control group.

Material was also available from seventeen patients with rheumatoid arthritis to whom iron had been given therapeutically. The results of the analyses of these tissues are compared with those of the untreated cases in Table VI (overleaf). Increased deposits of iron were found in all tissues examined, the increase being greatest in liver, spleen, and

TABLE V

MEAN TISSUE IRON CONTENT IN MATERIAL FROM PATIENTS WITH RHEUMATOID ARTHRITIS AND FROM CONTROLS

Tissue	Mean Values for Tissue Iron in Seven Patients with Rheumatoid Arthritis NOT Treated with Iron		Mean Concentration of Tissue Iron in Control Groups 1 to 3	
	mg. Fe/100 g. Wet Weight Tissue ± S.D.	No. of Observations	mg. Fe/100 g. Wet Weight Tissue ± S.D.	No. of Observations
Liver	20·0 ± 11·2	7	15·2 ± 6·0	35
Spleen	21·8 ± 10·3	7	21·7 ± 7·9	35
Kidney	3·3 ± 1·5	7	4·1 ± 0·9	33
Suprarenal	3·3 ± 0·6	7	3·6 ± 0·8	29
Lymph Node	4·7 ± 3·1	7	2·6 ± 0·8	19
Cardiac Muscle	1·8 ± 1·5	4	2·9 ± 2·5	16
Skeletal Muscle	1·0 ± 0·4	3	2·1 ± 1·2	14
Brain	3·4 ± 1·8	5	1·7 ± 0·7	6
Pancreas	1·5 ± 0·7	5	1·5 ± 0·7	15
Thyroid	0·9 ± 0·3	5	1·0 ± 0·2	10
Lung	3·6 ± 1·2	4	4·8 ± 2·7	19
Pituitary	2·1 —	1	1·7 —	1
Ovary	0·6 —	1	1·1 —	1
Testes	5·0 —	2	—	
Salivary Gland	1·2 ± 0·4	3	—	

TABLE VI

MEAN VALUES FOR TISSUE IRON
Expressed as mg. Fe/100 g. wet weight of tissue: ± S.D.: N = Number of Observations

Group		Sex	Age (yrs)	Tissue Iron									
				Liver		Spleen		Lymph Node		Lung		Suprarenal	
				mg./100 g.	N	mg./100 g.	N	mg./100 g.	N	mg./100 g.	N	mg./100 g.	N
Rheumatoid Arthritis	Not Given Fe	Total	60	20·0±11·2	7	21·8±10·3	7	4·7±3·1	7	3·6±1·2	4	3·3±0·6	7
		Female	63	15·5	4	17·1	4	3·9	4	2·7	2	3·3	4
		Male	54	26·0	3	28·1	3	5·8	3	4·5	3	3·3	3
	Given Fe or Transfusion	Total	60	70·0 —	17	127·8 —	16	21·3 —	16	8·3 —	7	11·7 —	13
		Female	61	84·7	11	126·9	10	26·5	10	8·4	5	11·8	8
		Male	60	73·1	6	130·9	6	12·7	6	8·3	2	11·6	5
Controls grouped according to Diagnosis	1	Total	34	11·1± 6·0	10	11·5± 6·8	10	1·7±0·8	6	2·3±0·8	4	3·8±1·7	10
		Female	43	8·6	3	9·1	3	1·9	3	1·9	1	4·9	3
		Male	30	12·1	7	12·3	7	1·5	3	2·5	3	3·3	7
	2	Total	66	16·9± 6·7	16	22·2±11·8	16	2·9±1·2	10	5·5±2·3	8	3·5±1·1	12
		Female	66	15·5	8	20·8	8	2·7	5	6·1	4	3·2	6
		Male	66	18·3	8	23·7	8	3·1	5	5·2	4	3·9	6
	3	Total	66	17·2± 6·5	9	32·1± 8·5	9	3·3±0·4	3	5·4±2·6	7	3·5±0·9	7
		Female	70	14·9	2	29·7	2	2·9	1	4·3	1	3·9	2
		Male	64	17·9	7	32·7	7	3·6	2	5·6	5	3·4	5
	4	Total	53	238·1 —	8	97·6 —	8	67·4 —	6	6·2 —	3	4·2 —	4
	1–3	Total	51	15·2± 6·0	35	21·7± 7·9	35	2·6±0·8	19	4·8±2·7	19	3·6±0·8	29

lymph nodes. Division of this group into those receiving iron orally, intravenously, or intramuscularly, and those receiving blood by transfusion revealed a difference in distribution of the additional iron. Whereas in both groups the hepatic iron content was increased by a factor of 3·5, the splenic iron content was increased by a factor of 5 in the former group and of 10 in the latter. In lymphatic tissues the opposite was found, the greatest increase being in the tissues from the patients to whom iron had been given orally, intravenously, or intramuscularly.

The mean weights of the liver and spleen from thirty fatal cases of rheumatoid arthritis were contrasted with those from thirty control cases of comparable age and sex (Table VII).

TABLE VII

COMPARISON BETWEEN MEAN WEIGHTS OF LIVER AND SPLEEN IN THIRTY CASES OF RHEUMATOID ARTHRITIS AND IN THIRTY CONTROL PATIENTS OF COMPARABLE AGE AND SEX DYING FROM SIMILAR CAUSES

Series	Weight (g.)	
	Spleen	Liver
Rheumatoid Arthritis Patients ..	224	1,490
Control Cases	120	1,435
Difference between Means	104	55
Standard Error of Difference ..	26·1	86

The results showed that the mean weights of the liver in the two groups did not differ significantly, but that the mean weight of the spleen in the cases of rheumatoid arthritis was significantly greater than that in the control group.

On the basis of this analysis, and in view of the results of the chemical estimations, it is suggested tentatively that the spleen in rheumatoid arthritis may contain appreciably more iron than is normal in healthy individuals of the same age.

Control Groups.—Iron was found in high concentration in the liver and spleen, only small amounts being present in other tissues. Analyses of the results suggested that the concentration of iron in the tissues increased with advancing age, the correlations reaching greater significance in the case of the spleen than in that of the liver (spleen: $p = 0{\cdot}001$, liver: $p = 0{\cdot}02$). There was also a tendency for more iron to be stored by males than by females. The mean iron content of liver and spleen in the male group were 16·4 and 22·9 mg./100 g., and in the female group 13·7 and 19·2 mg./100 g. respectively. This difference was emphasized by the fact that the male group was younger (mean age 52 years) than the female group (mean age 62 years).

The cases in groups 2 and 3 were originally chosen for comparison with the cases of rheumatoid

arthritis. Analyses of the results in the individual groups revealed that the mean tissue iron concentrations increased from group 1, to group 2, to group 3. These differences reached the level of significance for liver of $p = 0{\cdot}02$, and for spleen of $p = 0{\cdot}001$ when groups 1 and 3 were compared. If, however, the mean ages of these two groups (34 and 66 years respectively) were taken into account, the apparently increased storage of iron with increasingly severe disease could be explained simply on the basis of advancing age.

As might be anticipated from previous reports of the iron content of tissues in iron storage diseases, the mean values obtained in group 4 were greatly increased by contrast with the other groups, irrespective of age.

Discussion

The storage of iron in body tissues in some human diseases has been sporadically investigated (Sheldon, 1935; Cappell, Hutchison, and Jowett, 1957). In health, the liver and the spleen are known to be the principal sites of iron storage and it is believed that 95 to 97 per cent. of such iron is available for haemoglobin synthesis (Finch, Hegsted, Kinney, Thomas, Rath, Haskins, Finch, and Fluharty, 1950). It seems reasonable to suppose that the liver and spleen in rheumatoid arthritis may contain a greater amount of iron than normal, since it is known that in this disease the red cells are hypochromic while the capacity to absorb iron from the small intestine is not impaired (Roy and others, 1955).

In the present investigation a comparison was made between the concentration of iron in the organs of the reticulo-endothelial system from cases of rheumatoid arthritis and that in those from cases selected to provide suitable control material. The spectrum of control cases was chosen to include young, healthy individuals, older persons dying unexpectedly, and persons of the same mean age as the group with rheumatoid arthritis dying from similar causes. As a result of this division it became clear that allowance must be made for the influence of age and sex on tissue iron concentration. It was shown that the concentration of iron in the liver and spleen of persons with rheumatoid arthritis was not significantly higher than that in controls of similar mean age dying from analogous causes. The iron concentration in lymph nodes, suprarenals, and lungs from cases of rheumatoid arthritis was also not significantly raised.

There is therefore no evidence to support the suggestion that the main iron storage organs in rheumatoid arthritis contain a greater concentration of iron than is usually the case. At the same time, histological examination of those tissues containing elements of the reticulo-endothelial system has provided no easily measurable evidence of reticulo-endothelial hyperplasia or of reticulo-endothelial overactivity. However, there is an impression of hyperplasia of germinal follicles of the lymph nodes in many parts of the body and of the spleen. It is impossible to estimate the volume of lymphoid tissue in lymph nodes and throughout the viscera. Whether it is present in excess in rheumatoid arthritis is therefore not known, but measurement of weight has indicated that the spleen in rheumatoid arthritis is significantly larger than in control persons of the same age and sex. This suggests that the large spleen may contain a greater absolute amount of iron than usual and that the spleen may act as a reservoir for the iron absorbed, but not used in haemoglobin synthesis.

This interpretation must be viewed with some reserve. With the exception of the spleen, there is no suggestion of excessive storage of iron in rheumatoid arthritis. Low serum iron and the absence of stainable iron from the bone marrow may be explained by faulty absorption from the gut or excessive excretion of iron by the kidneys. The evidence at present available lends no support to these theories (Roy and others, 1955). It appears possible that further studies with labelled iron compounds may throw additional light on this problem. The present results may be regarded as providing an impetus to the extension of such observations.

Summary

Samples of liver, spleen, lymph node, lung, and suprarenal were collected at necropsy from 34 patients with rheumatoid arthritis who died in hospital. Similar samples were obtained from 43 control cases who died from other causes. The control cases were chosen in such a way that the influence of age and of sex on the tissue iron concentration could be assessed. The organs were examined histologically for iron by the Prussian blue reaction. Comparable tissue samples were analysed chemically for non-haem iron.

The concentration of iron in the liver, spleen, lungs, lymph nodes, and suprarenals in cases of rheumatoid arthritis not known to have received treatment with iron therapeutically or blood by transfusion was compared with that in the same organs of control cases. No difference in tissue iron concentration was found which could not be explained by invoking the demonstrated increase of storage iron with age, particularly in the male.

Histological examination of the organs of the reticulo-endothelial system revealed no satisfactory

evidence for the nature of the hyperplasia or over-activity of this system which has been suggested as a likely explanation for the abnormal rapidity with which injected saccharated oxide of iron is removed from the plasma in patients with rheumatoid arthritis. Evidence of lymphoid hyperplasia was provided by the demonstration of significant splenic enlargement.

On the basis of this splenic enlargement it is tentatively suggested that the spleen may contain approximately twice as much iron in this disease as is normally the case. Proof of this suggestion must await chemical analyses of total splenic iron in further cases of rheumatoid arthritis.

The advice and encouragement of Prof. G. L. Montgomery and of Dr. J. J. R. Duthie are gratefully acknowledged.

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REFERENCES

Cappell, D. F., Hutchison, H. E., and Jowett, M. (1957). *J. Path. Bact.*, **74**, 245.

Cartwright, G. E., and Wintrobe, M. M. (1952). *Advanc. intern. Med.*, **5**, 165.

Finch, C. A., Hegsted, M., Kinney, T. D., Thomas, E. D., Rath, C. E., Haskins, D., Finch, S., and Fluharty, R. G. (1950). *Blood*, **5**, 983.

Freireich, E. J., Ross, J. F., Bayles, T. B., Emerson, C. P., and Finch, S. C. (1957). *J. clin. Invest.*, **36**, 1043.

Gardner, D. L. (1958). *Stain Technol.*, **33**, 295.

Kerr, L. M. H. (1957). *Biochem. J.*, **67**, 627.

Marshall, A. H. E. (1956). "An Outline of the Cytology and Pathology of the Reticular Tissue", p. 258. Oliver and Boyd, Edinburgh.

Ramsay, W. N. M., and Campbell, E. A. (1954). *Biochem. J.*, **58**, 313.

Richmond, J., Gardner, D. L., Roy, L. M. H., and Duthie, J. J. R. (1956). *Ann. rheum. Dis.*, **15**, 217.

Roy, L. M. H., Alexander, W. R. M., and Duthie, J. J. R. (1955). *Ibid.*, **14**, 63.

Sheldon, J. H. (1935). "Haemochromatosis." Oxford University Press, London.

Sinclair, R. J. G., and Cruickshank, B. (1956). *Quart. J. Med.*, **n.s. 25**, 313.

Fer tissulaire et système réticulo-endothélial dans l'arthrite rhumatismale

RÉSUMÉ

On étudia les prélèvements de foie, rate, ganglions lymphatiques, poumon et surrénale, effectués à l'autopsie de 34 malades atteints d'arthrite rhumatismale décédés à l'hôpital. Des prélèvements similaires furent obtenus chez 43 témoins morts de diverses autres causes. Les témoins furent choisis de manière à permettre une étude comparée de l'influence de l'âge et du sexe sur le taux ferrique tissulaire. Histologiquement, le fer fut recherché dans les organes à l'aide du bleu de Prusse. Des échantillons comparables furent examinés chimiquement pour déterminer le fer non-hématique.

Le taux de fer dans le foie, la rate, les poumons, les ganglions lymphatiques et dans les surrénales des cas d'arthrite rhumatismale, n'ayant pas reçu, autant qu'on sache, de thérapie martiale ou de transfusion sanguine, fut comparé à celui dans les mêmes organes des témoins. On ne trouva dans les taux de fer tissulaire que des différences attribuables à l'emmagasinage augmenté de ce métal avec l'âge, surtout chez les hommes.

Les examens histologiques des organes du système réticulo-endothélial ne révélèrent rien qui puisse expliquer d'une manière satisfaisante la nature de l'hyperplasie ou de l'activité exagérée de ce système, invoquées comme causes possibles de la vitesse anormale avec laquelle l'oxyde saccharé de fer, injecté aux malades atteints d'arthrite rhumatismale, est éliminé de leur plasma. L'hyperplasie lymphoïde fut prouvée par le fait que la rate était appréciablement augmentée de volume.

Cette augmentation du volume splénique nous fait penser que dans cette maladie la rate peu bien contenir deux fois plus de fer qu'une rate normale. Pour prouver cette hypothèse on devra attendre les résultats de l'analyse chimique du fer splénique total dans d'autres cas d'arthrite rhumatismale.

Hierro tisular y el sistema reticulo-endotelial en la artritis reumatoide

SUMARIO

Se recogieron muestras de hígado, bazo, ganglios linfáticos, pulmón y suprarrenales en necropsias de 34 enfermos con artritis reumatoide fallecidos en hospital. Muestras similares se obtuvieron en 43 testigos que fallecieron de otras diversas causas. Los testigos fueron elegidos de tal forma que la influencia de la edad y el sexo en la concentración de hierro tisular pudiera ser estudiada comparativamente. El hierro de los órganos se investigó histológicamente con la reacción del azul de Prusia. Muestras comparables se examinaron químicamente para determinar el hierro no hemático.

La concentración de hierro en hígado, bazo, pulmones, ganglios linfáticos y suprarrenales en casos de artritis reumatoide, en los que se conocía no haber recibido terapéutica férrica, directa o por transfusión sanguínea, se comparó con la hallada en los mismos órganos de los testigos. No se encontró ninguna diferencia en la concentración tisular de hierro que no fuese explicable por el demostrado incremento de almacenaje de hierro con la edad, especialmente en el varón.

Exámenes histológicos de órganos del sistema retículo-endotelial no produjeron datos para explicar satisfactoriamente la naturaleza de la hiperplasia o hiperactividad de dicho sistema, aducida como causa posible de la abnormal rapidez con que es eliminado del plasma el óxido sacarado de hierro inyectado en enfermos con artritis reumatoide. Prueba de la existencia de hiperplasia linfoidea fué encontrada en el significativo aumento del volumen del bazo.

Dicho aumento del volumen esplénico induce a pensar que el bazo pude contener, en casos de esta enfermedad, doble de la cantidad de hierro presente normalmente. Prueba de tal hipótesis debe esperar el análisis químico de la cantidad total de hierro esplénico en otros casos de artritis reumatoide.

Ann. rheum. Dis. (1961), **20**, 265.

IMMUNO-ELECTROPHORETIC ANALYSIS OF PROTEINS IN SERUM AND SYNOVIAL FLUID IN RHEUMATOID ARTHRITIS AND ANKYLOSING SPONDYLITIS

BY

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Among the systemic manifestations of rheumatic disease it is customary to include a number of quantitative changes in the constituents of plasma, together with abnormalities in immunological and other properties of serum. Although most of these changes are neither uniquely nor constantly demonstrable in this group of diseases or in any member of the group, it is likely that information on the true nature of the underlying changes in plasma constituents will contribute to an understanding of the fundamental significance of these phenomena.

A complete list of all the changes so far recorded is not relevant to this report, but among those more frequently demonstrable may be included an increase in the total gamma globulin, and in alpha-1 and alpha-2 glycoproteins as shown by paper electrophoresis, elevation of the erythrocyte sedimentation rate, and the presence of demonstrable amounts of one or more "rheumatoid factors", having in common the property of reacting with denatured gamma globulin.

One or more fractions reacting *in vitro* with nuclear material are demonstrable in sera from a minority of patients with rheumatoid arthritis, and also from the majority of patients with systemic lupus erythematosus, in whom a number of other serum factors have been described which react *in vitro* with more or less denatured constituents of cells or organs.

The immuno-electrophoretic technique of Grabar and Williams (1953) provides an approach to the problem of exploring the nature of abnormally reactive components in serum and other body fluids, in that it permits the identification and separation of a far larger number of distinct protein fractions than is possible by any other method used alone. The nature of the physiological properties of many of these fractions remains unknown, and indeed it would be unreasonable to conclude at present that fractions identified from their associated electrophoretic and antigenic properties are necessarily also functional entities. Nevertheless, it is likely that immuno-electrophoretic techniques can now provide qualitative and semi-quantitative data on the constituents of serum in health and disease which may ultimately be integrated with the results obtained by exploration of the functional characteristics of whole serum and its constituent proteins.

Schmid and MacNair (1956) were the first to use immuno-electrophoretic techniques to study the proteins of serum and synovial fluid from patients with rheumatic diseases; they confirmed that the individual proteins from these two sources had similar electrophoretic and antigenic properties.

Increased amounts of alpha-1 and alpha-2 glycoproteins and beta-2 macroglobulin were found in sera from patients with rheumatoid arthritis or rheumatic fever by Cleve and Hartmann (1957) and by Cleve (1958). No correlation was apparent between the increase in beta-2 macroglobulin and the Rose-Waaler haemagglutination titre in the sera from patients with rheumatoid arthritis, and the protein changes in this disease and in rheumatic fever were interpreted as a manifestation of active inflammation. The authors also investigated the proteins in synovial fluid where the concentration of fractions of high molecular weight was lower than in serum.

Increased amounts of alpha-2 glycoproteins (*i.e.* haptoglobin and alpha-2 macroglobulin) in the serum of patients with rheumatoid arthritis were also reported by Fenrych, Jazienicki, Mackiewicz, Mackiewicz, and Twardowski (1959). Moreover, the latter component was increased in twenty of the 42 sera from patients with various forms of chronic

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arthritis examined by Francq, Eyquem, Podliachouk, and Jacqueline (1959). By specially prepared antisera, the authors demonstrated a correlation between the increase in beta-2 macroglobulin and gamma globulin, and the titre for agglutination of sensitized sheep erythrocytes.

From the foregoing it is evident that increased amounts of certain fractions of the alpha and beta globulins and of gamma globulins are frequently demonstrable in sera from patients with rheumatoid arthritis, although the relationship between these changes and other manifestations of the disease remains uncertain.

The present report is concerned with further attempts to characterize changes in protein fractions in serum and synovial fluid associated with rheumatoid arthritis.

Material and Methods

The sera investigated were obtained from 43 patients with rheumatoid arthritis and 22 with ankylosing spondylitis and from twenty healthy individuals (with a normal paper electrophoresis pattern). The patients with rheumatoid arthritis included eighteen men and 25 women between the ages of 22 and 65 years, the duration of disease being between 1 and 15 years. The diagnosis was based upon typical clinical findings and confirmed by radiography of the joints. Two patients in this group also had chronic renal functional impairment with oedema and proteinuria, and in one of the two the presence of amyloidosis was demonstrated by a modification of the congo red test of Bennhold (Chodera and Mackiewicz, 1958), and by gum biopsy. The haemagglutination test of Rose and Heller was performed on sera from twelve of the patients with rheumatoid arthritis, and the titre was significantly raised in each of them.

The group of patients with ankylosing spondylitis included twenty men and two women between the ages of 24 and 57, the duration of disease being between 2 and 9 years. The diagnosis was made from clinical findings and radiological evidence of bilateral sacro-iliitis; in two patients there was a previous history of rheumatic fever and in one there were signs of mitral stenosis and incompetence. Sera from eight of these patients were tested by the method of Rose and Heller and in all of them the haemagglutination titre fell within the normal range.

The erythrocyte sedimentation rate (E.S.R.) was measured by the Westergren method in all patients in the rheumatoid and spondylitie groups. In eleven it exceeded 100 mm./hr, in seventeen it was between 60 and 99 mm./hr, and in the remaining 37 it was between 40 and 59 mm. in the first hour. Thus all the patients showed a significant elevation, and from this and other evidence it was concluded that they all had active disease. The haemoglobin and erythrocytes were determined in the blood of these patients in an automatic apparatus. A normochromic or hypochromic anaemia was present in nine patients with rheumatoid arthritis and in six with ankylosing spondylitis.

In the sera from patients and healthy subjects, total protein was determined by the biuret method and the major protein fractions by filter paper electrophoresis.

All immuno-electrophoretic studies on sera in these investigations were performed in duplicate. Synovial fluids obtained from the knee joints of a number of the patients with rheumatoid arthritis were also subjected to immuno-electrophoresis, as were samples of urine from the two patients with renal disease. In the immuno-electrophoretic procedure the sera, synovial fluid, and urine were studied in terms of their antigenic constituents. The antisera included polyvalent rabbit antihuman serum prepared by immunizing animals with whole human serum either pooled or from individuals, following the procedure described by Cleve and Hartmann (1957). Two rabbits were immunized with serum from normal subjects, two with serum from the two patients with renal disease, and eight with sera of a high haemagglutination titre obtained from patients with rheumatoid arthritis. Two of the latter eight rabbits showed signs such as loss of weight, roughening of the fur, and ultimately paralysis of the hindquarters. Histological examination of tissues obtained from those rabbits at autopsy showed widespread arteritis, together with diffuse glomerulitis, the lesions being similar to those previously observed in mice and rats after the intravenous administration of soluble antigen-antibody complexes (McCluskey, Benacerraf, Potter, and Miller, 1960; Benacerraf, Potter, McCluskey, and Miller, 1960).

The remaining ten rabbits showed no adverse effects from immunization. After immunization the rabbits were bled from the carotid artery and the antisera obtained were tested initially by double-diffusion in agar with whole or fractionated human serum (Ouchterlony, 1953). When used in immuno-electrophoresis the antisera produced at least fourteen and as many as nineteen distinct precipitin lines with a variety of human sera. There was no constant difference in the number of lines produced with the antisera prepared against normal human serum, and the number produced with the antisera against serum from patients with rheumatoid arthritis.

The known antigenic components of serum represented by the precipitin arcs were identified by their characteristic distribution on immuno-electrophoresis, by means of specific univalent antisera to individual components of serum (obtained from Behring and Co. Ltd., Marburg-Lahn), and by the use of differential staining techniques for lipoprotein. The following univalent antisera were used: anti-prealbumin, anti-albumin, anti-alpha-2 macroglobulin, anti-alpha-2 lipoprotein, anti-beta-1 lipoprotein, and anti-gamma globulin.

Sera obtained from the rheumatic patients were compared with those from healthy subjects in terms of the number and intensity of precipitin lines apparent after electrophoresis followed by double diffusion with particular antisera. Two of the sera from healthy individuals were chosen as standards of normality and all others were compared with these in terms of the

presence of particular immuno-electrophoretic components and on the basis of comparative quantitation of these components. To measure the relative concentrations of a particular component in two different sera, aliquots of antiserum were absorbed with varying amounts of one serum. The absorbed aliquots were then tested in immuno-electrophoresis to determine the amount of the absorbing serum sufficient to prevent formation of a precipitin line corresponding with the component in question. Thus a relatively higher concentration of a particular antigen in one of the two sera was reflected by the relatively smaller volume of serum required to absorb the specific antibody. The procedures followed in the present studies were evolved on the basis of this principle, but were necessarily simplified in order to permit the analysis of a large number of sera. As an alternative and more satisfactory method for semi-quantitative determination of the relative concentrations of components in two sera, polyvalent and univalent antisera were set up against several dilutions of both, and the dilution which prevented formation of the particular precipitate was recorded for each serum. The serum requiring more dilution for this effect was considered to have a higher concentration of the component in question.

The immuno-electrophoretic technique is a modification, introduced by Fenrych and others (1959), of the micro-method described by Scheidegger (1955). Electrophoretic separation of the sera was produced in 2 per cent. agar-gel in barbiturate buffer pH 8·2; 0·1 M. on microscope slides measuring 26 × 76 mm. The serum was inserted in a round well (0·9 mm.) placed centrally. After electrophoretic separation, antisera were inserted into longitudinal troughs (36 × 1 mm.) cut in the gel near one or both sides of the slide and parallel to the axis of electrophoretic migration. In this system lines of precipitate appear at the interfaces between components of serum diffusing outwards from the axis of electrophoretic migration and their specific antibodies diffusing inwards from the troughs containing antiserum. The position, shape, and density of the precipitates so formed are determined by the interaction of factors, including electrophoretic mobility of antigen, the diffusion constants of antigen and antibody, the relative concentrations of these reagents, and their optimum combining ratios. The large number of distinct precipitates formed with a complex system of antigens and antibodies depends upon the extremely low probability that two or more antigen-antibody pairs in the system will be identical in so many different respects.

Results

The characteristic immuno-electrophoretic components of human serum are shown in Fig. 1, which, for clarity, is a diagram based upon the precipitin patterns identified with this technique. In this diagram the components are named according to the terminology of Grabar (1960). The alpha-2 lipoproteins are further subdivided into "fast" and "slow" components, and "alpha-1 principale" (S_{20} = 3·5 Sv.) is designated "main alpha-1". The precipitates so far identified are labelled, and it should be noted that the components do not form groups limited to the major bands produced by simple electrophoresis. This may result from the free radial diffusion of all components occurring in immuno-electrophoresis during the phase necessary for formation of the specific precipitates. Such diffusion complicates the interpretation of the results of immuno-electrophoresis in terms of those of simple electrophoresis, and the two methods of analysis are complementary rather than equivalent.

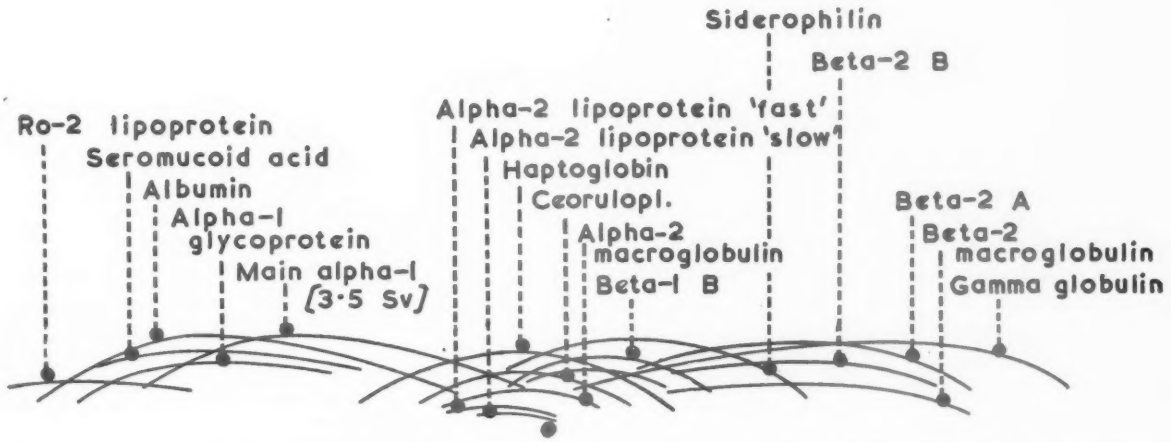

Fig. 1.—Immuno-electrophoretic components of serum. Diagram constructed from a number of studies and including the components so far identified.

TABLE

COMPARISON OF RESULTS OF IMMUNO-ELECTROPHORESIS WITH THOSE OF PAPER ELECTROPHORESIS

Groups of Subjects		No. of Individuals	Increase of Alpha-1 globulins				Increase of Alpha-2 globulins						Increase of Beta-2 macroglobulin and Gamma globulin			
			Immuno-electrophoresis Acid Seromucoid		Paper Electrophoresis Total Alpha-1 globulin		Immuno-electrophoresis				Paper Electrophoresis Total Alpha-2 globulin		Immuno-electrophoresis Beta-2 macroglobulin		Paper Electrophoresis Gamma globulin	
							Haptoglobin		Alpha-2 macroglobulin							
			No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
(1) Rheumatoid Arthritis (Functional Capacity)	Grade I	8	4	50	2	25	5	63	4	50	5	63	5	63	5	63
	Grade II	18	12	67	3	17	13	72	10	56	9	50	15	83	18	100
	Grade III	13	7	54	2	16	10	77	6	46	6	46	11	85	10	77
	Grade IV	4	1	25	0	0	2	50	2	50	1	25	3	75	4	100
	All Grades	43	24	56	7	16	30	70	22	51	21	47	35	81	37	86
(2) Ankylosing Spondylitis ..		22	6	27	3	14	13	59	10	45	5	23	15	68	17	77
(3) Normal Subjects		20	2	10	0	0	0	0	2	10	0	0	3	15	0	0

For this reason data obtained by both the methods presented in the Table are arranged to show the semiquantitation of immuno-electrophoretic components alongside quantitation of the major electrophoretic fractions likely to include part or all of these components.

Except in the case of albumin and gamma globulin, which are relatively homogenous, there was little or no quantitative correlation between the immuno-electrophoretic components and the corresponding major protein fractions, at least in terms of the observed differences between sera obtained from healthy individuals or patients, and the standard sera obtained from the other healthy individuals. Excessive amounts of individual components were observed more frequently in the sera of rheumatic patients than in those of healthy individuals, but these changes were not clearly related either to other features of rheumatoid arthritis, such as elevation of the erythrocyte sedimentation rate or severity of the disease in terms of functional impairment, or to duration of the disease. No attempt will be made to interpret the following changes observed in presently identified immuno-electrophoretic components of the major electrophoretic fractions.

Pre-albumin.—Ro-2 lipoprotein is a component of pre-albumin. The latter fraction is usually found in barely detectable quantities, if at all, in normal serum. The ro-2 lipoprotein was readily demonstrated in the sera from four patients with rheumatoid arthritis, including the two with complicating renal disease, and it was also demonstrable in the serum of one of the patients with ankylosing spondylitis. The fraction was more readily demonstrable with the antisera prepared against the serum of patients with renal disease, because of the presence of relatively greater amounts of the appropriate antibody.

Albumin.—This was represented by a single precipitin line produced by all the sera tested, but the density of the precipitate varied in the proportion to the concentration of albumin determined by paper electrophoresis (Figs 2, 3, 4, opposite, and Fig. 5, overleaf).

Alpha-1 Globulin.—Increased amounts of acid seromucoid were found in 24 (56 per cent.) of the sera obtained from the patients with rheumatoid arthritis, in six (27 per cent.) of those from the patients with ankylosing spondylitis, and in two (10 per cent.) of those from healthy individuals. Although there was much variation in the density of the precipitin lines of other components of this fraction, no consistent pattern could be discerned (Fig. 2).

Alpha-2 Globulin.—All the sera from the patients with rheumatoid arthritis and sixteen (75 per cent.) of those from the patients with ankylosing spondylitis gave rise to precipitin lines of markedly increased density corresponding with components of alpha-2 globulin (Figs 2 and 4). On the basis of the semiquantitative procedures, thirty (70 per cent.) of the sera from patients with rheumatoid arthritis contained increased amounts of the haptoglobin component and 22 (51 per cent.) of these sera also contained increased amounts of the alpha-2 macroglobulin component (Figs 2 and 4). The sera from patients with rheumatoid arthritis containing increased amounts of alpha-2 macroglobulin included

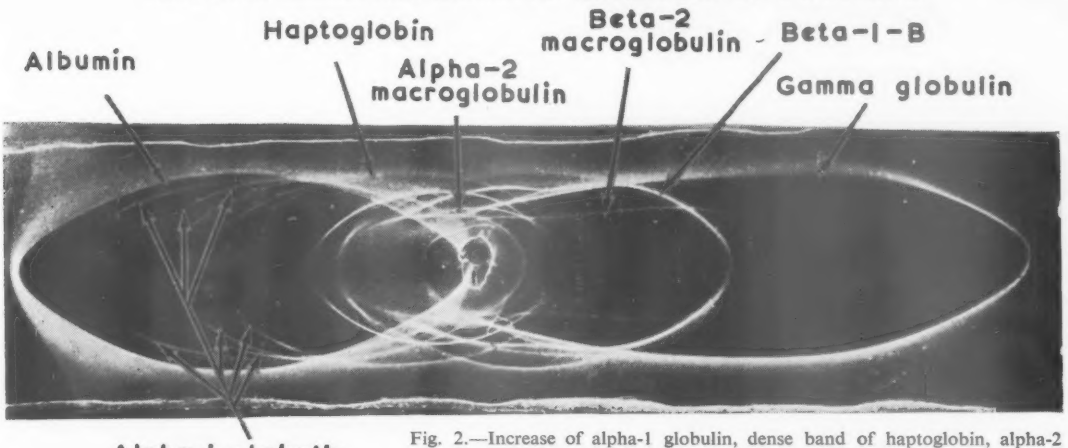

Fig. 2.—Increase of alpha-1 globulin, dense band of haptoglobin, alpha-2 macroglobulin, beta-2 macroglobulin, and beta-1-B globulin.

Antiserum: Rabbit-antihuman-rheumatoid serum.
Antigen: Serum from patient with rheumatoid arthritis (functional capacity Grade II, E.S.R. 110 to 127 mm./hr, haemagglutination titre 1 : 1,024).
Paper Electrophoresis: Albumin 39·0 per cent., Alpha-1 globulin 5·4 per cent., Alpha-2 globulin 12·3 per cent., Beta-1 globulin 11·2 per cent., Gamma globulin 32·1 per cent.

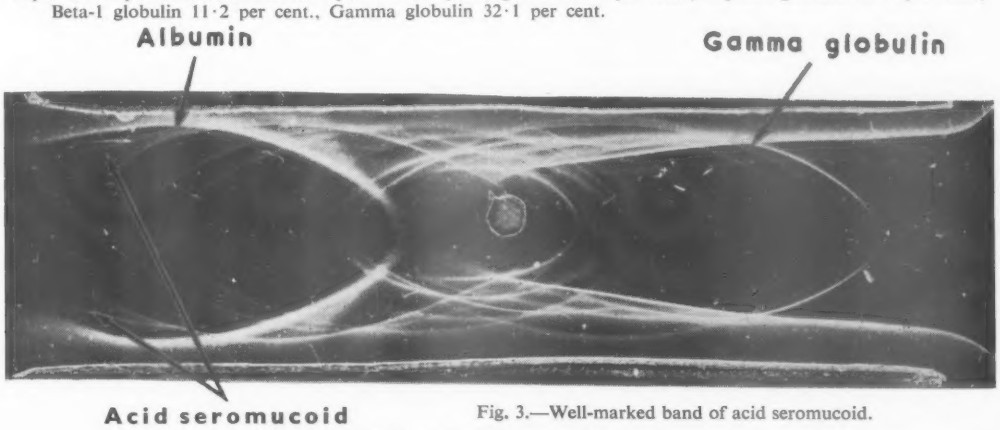

Fig. 3.—Well-marked band of acid seromucoid.

Antiserum: Rabbit-antihuman-rheumatoid serum.
Antigen: Synovial fluid from the same patient as in Figure 2.

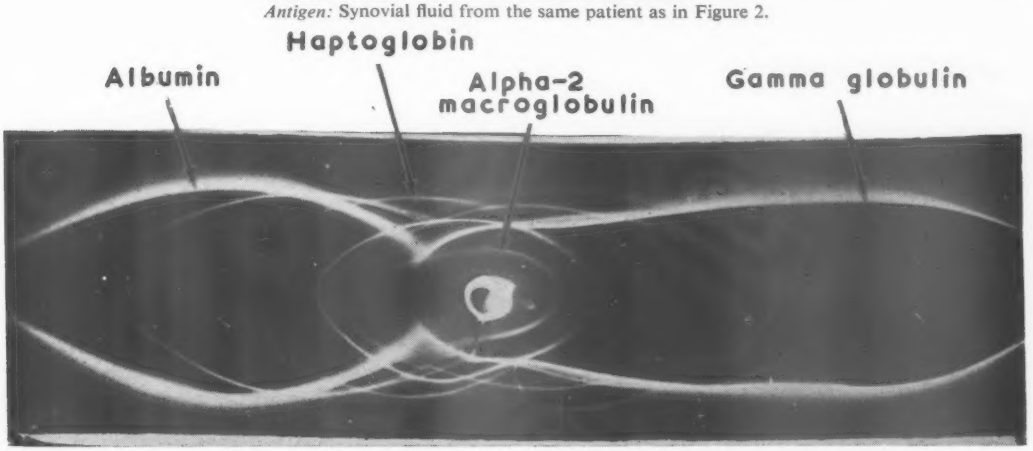

Fig. 4.—Dense band of haptoglobin, alpha-2 macroglobulin, and beta-2 macroglobulin.

Antiserum: Rabbit-antihuman-rheumatoid serum.
Antigen: Serum from patient with rheumatoid arthritis (functional capacity Grade III, E.S.R. 60 to 90 mm./hr, haemagglutination titre 1 : 64).
Paper Electrophoresis: Albumin 48·0 per cent., Alpha-1 globulin 4·7 per cent., Alpha-2 globulin 9·0 per cent., Beta globulin 11·8 per cent., Gamma globulin 26·2 per cent.

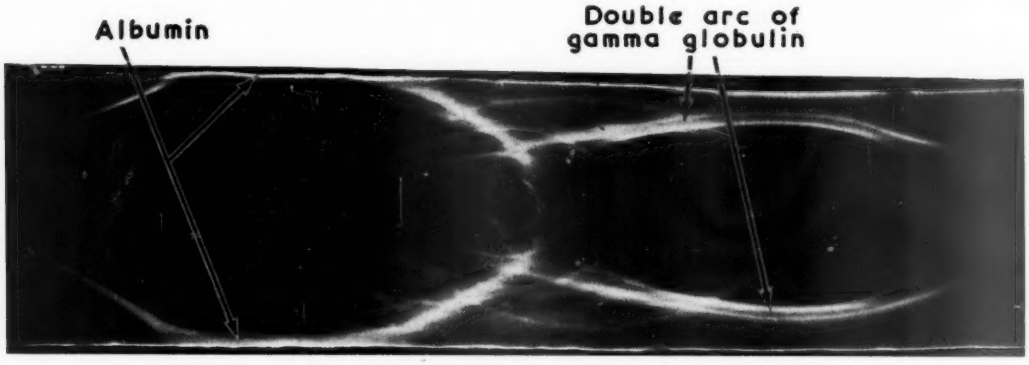

Fig. 5.—Double arc of gamma globulin.
Antiserum: Rabbit-antihuman-rheumatoid serum.
Antigen: Serum from patient with rheumatoid arthritis (functional capacity Grade III, E.S.R. 110 to 125 mm./hr, haemagglutination titre 1 : 1,024).
Paper Electrophoresis: Albumin 40·5 per cent., Alpha-1 globulin 4·3 per cent., Alpha-2 globulin 9·9 per cent., Beta-globulin 11·3 per cent., Gamma globulin 34·0 per cent.

those from two patients with renal disease, in whose sera alpha-2 lipoprotein was also demonstrable. This component was subdivided into two moities differing slightly in their electrophoretic mobility (*i.e.* "slow" and "fast").

Beta-1 Globulin.—A dense precipitate of beta-1-B globulin was produced with seven of the sera from patients with rheumatoid arthritis by the rabbit antisera to serum from patients with renal disease (Fig. 2). Increased amounts of beta-1 lipoprotein were present in the serum of these two patients.

Beta-2 Globulin.—Three components of this fraction were identified as beta-2 A, beta-2 B, and beta-2 M. There was evidence of a fourth component in this fraction of the sera obtained from four of the healthy individuals. This precipitate appeared only when these were tested with rabbit antiserum prepared against serum from the patients with renal disease. The component has not yet been identified.

The precipitates attributed to the A and B components varied too much to permit adequate description, and only the M component will be considered. This was increased in 35 (81 per cent.) of the sera obtained from patients with rheumatoid arthritis, in fifteen (68 per cent.) of those from patients with ankylosing spondylitis, and in three (15 per cent.) of those from healthy individuals (Figs 2 and 4).

Gamma Globulin.—This fraction usually has a single immuno-electrophoretic component. However, eight sera from the patients with rheumatoid arthritis and two from patients with ankylosing spondylitis produced an additional precipitin line, parallel to the first, suggesting the presence of two distinct antigenic components in the gamma globulin fraction (Fig. 5). This possibility is discussed later.

Synovial Fluid.—Proteins in the synovial fluids from eight patients with rheumatoid arthritis were examined by immuno-electrophoresis, and the concentrations of several components were compared with those of the same components of serum proteins. In six of the eight synovial fluids the concentration of alpha-2 and beta-1 lipoprotein and of beta-2 macroglobulin was significantly lower than in the corresponding sera. A dense band of precipitate corresponding with acid mucoprotein of serum was observed in the patterns produced by the synovial fluids obtained from three rheumatoid patients with active inflammatory features of recent onset (Fig. 3).

Urine.—In immuno-electrophoresis, urine from the two patients with rheumatoid arthritis and renal disease produced seven or eight distinct precipitin lines (Fig. 6, opposite). The samples of urine contained 7 to 18 g. protein per litre, and the components producing the most dense precipitates were identified as albumin, alpha-1 proteins, alpha-2 proteins, siderophilin, and gamma globulin.

Discussion

It is possible to measure the concentration of the major electrophoretic fractions of serum as percentages of the total protein in the sample, and to calculate absolute concentration from these data. Similar quantitation of immuno-electrophoretic components is not yet possible and although some information is provided by the intensity and position of the precipitates, these characteristics are partly determined by the antigenic potency of individual proteins. A number of proteins may be present in only small amounts (*e.g.* alpha-2 and beta-2 macroglobulins) and yet induce relatively large amounts

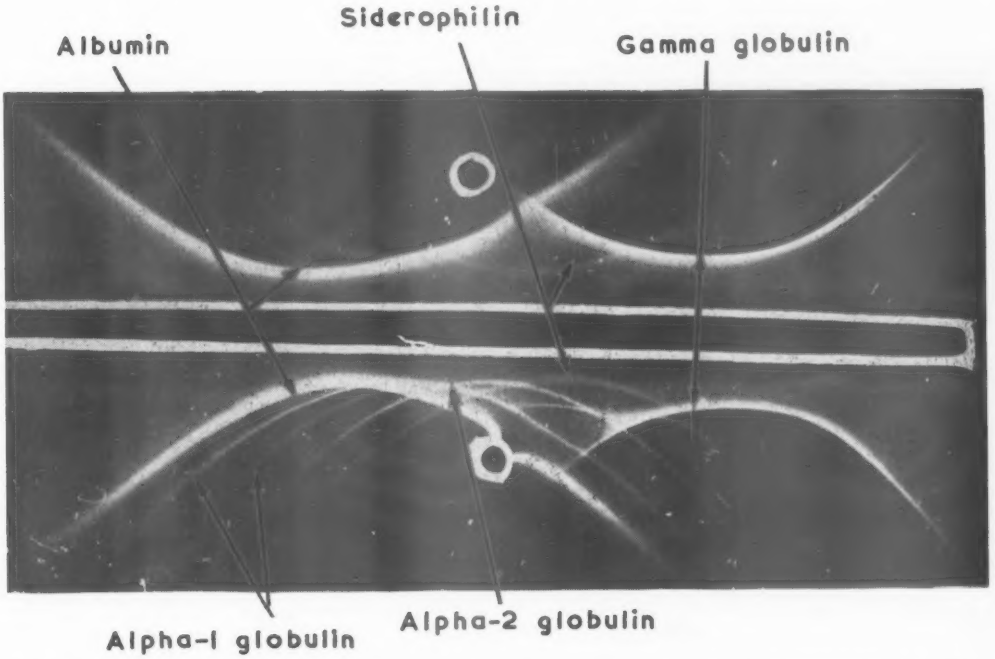

Fig. 6.—Upper: chronic nephrotic syndrome (proteinuria 18 g./litre). Lower: amyloidosis (proteinuria 15 g./litre).
Antiserum: Rabbit-antihuman-nephrotic serum.
Antigen: Urine from two patients with rheumatoid arthritis and renal disease.

of specific antibody in a polyvalent antiserum, with the consequent formation of dense precipitates on immuno-electrophoresis.

In the present investigations, quantitation of individual components relative to the same components in standard sera was attempted by methods involving dilution or selective absorption. The quantitative changes thus demonstrated in sera from patients with rheumatic disease were in general not paralleled by comparable changes in the major electrophoretic fractions, and it seems likely that paper electrophoresis and immuno-electrophoresis are complementary rather than interchangeable methods of analysis (Table).

All the abnormalities of serum proteins found on immuno-electrophoresis occurred in both rheumatoid arthritis and ankylosing spondylitis and with approximately the same incidence. The possibility remains that extended investigation may reveal differences between the two diseases in terms of serum proteins and their sub-fractions. However, the changes so far demonstrated appear to be non-specific manifestations of inflammation occurring in both diseases.

The most frequently observed abnormality was the presence of an increased amount of beta-2 macroglobulin; this was demonstrated in 81 per cent. of the sera from patients with rheumatoid arthritis and in 68 per cent. of those from patients with ankylosing spondylitis. This difference in incidence between the groups is not significant:

$$\chi^2 = 0{\cdot}8;\ 0{\cdot}5 > P > 0{\cdot}3.$$

The abnormality appears to be associated with active inflammation and has been previously observed in active rheumatoid arthritis by Cleve and Hartmann (1957), Cleve (1958), Fenrych and others (1959), Mackiewicz and Fenrych (1959), and Francq and others (1959). Because increased amounts of this macroglobulin were found in sera with a normal sheep cell agglutination titre and in those with a high titre, it is evident that the amount of beta-2 macroglobulin was unrelated to the presence or absence of rheumatoid factor. According to Burtin (1960), the beta-2 macroglobulin includes a number of proteins differing in physiological properties but having identical basic antigenic structures. The lack of correlation between the sheep cell titre and the concentration of the macroglobulin is therefore not evidence against the rheumatoid factor being a member of this family of proteins.

Many of the sera from rheumatic patients gave rise to precipitates of increased density in the bands identified as alpha-1 and alpha-2 glycoprotein, acid seromucoid, haptoglobin, and alpha-2 macroglobulin. Such changes were demonstrable with

sera from rheumatoid patients in all functional grades, but were less frequent with sera from spondylitic patients; their significance remains unknown.

The double precipitate of gamma globulin which occurred with some sera has been reported previously. While the double arc is unusual (Grabar and Williams, 1955) and may sometimes occur as an artefact due to temperature changes during diffusion, true duplication is a reproducible phenomenon when particular antisera are used. A double band produced by sera from infants and children was reported by Hitzig (1957) and by Giedion and Scheidegger (1957). In adults the anomaly was found by Schultze and Schwick (1957) in chronic hepatitis, chronic nephrosis, and reticulosis. A double gamma globulin precipitate was also produced by sera from patients with reticulosis (Creyssel, Fine, and Morel, 1959) and by sera from some patients with rheumatoid arthritis (Fenrych and others, 1959). Recently also, Grabar and Burtin (1960) emphasized the immunological heterogeneity of gamma globulin. The significance of such heterogeneity remains unknown and requires further investigation.

Summary

Immuno-electrophoretic analysis was performed on sera from 43 patients with rheumatoid arthritis and 22 patients with ankylosing spondylitis, on synovial fluid from eight patients with rheumatoid arthritis, and on urine from two patients with rheumatoid arthritis complicated by renal disease.

In many sera from patients with rheumatoid arthritis and ankylosing spondylitis there were increased amounts of alpha-1 and alpha-2 glycoproteins.

The most constant finding in both groups was an increased amount of beta-2 macroglobulin. In sera from some patients with rheumatoid arthritis and ankylosing spondylitis, a double arc of gamma globulin was found. The significance of this finding is discussed.

Immuno-electrophoretic patterns of synovial fluid and urine were compared with the patterns of sera from the same patients.

We are much indebted to Dr. J. L. Potter and Dr. J. J. R. Duthie for their helpful advice. We wish to thank Dr. P. Burtin from the Institut Pasteur, Paris, for helping to interpret some of the immuno-electrophoretic patterns.

REFERENCES

Benacerraf, B., Potter, J. L., McCluskey, R. T., and Miller, F. (1960). *J. exp. Med.*, **111**, 195.

Burtin, P. (1960). *In* "Ciba Foundation Symposium on Cellular Aspects of Immunity", p. 213. Churchill, London.

—— (1961). Personal communication.

Chodera, A. and Mackiewicz, S. (1958). *Przegl. lek.*, **14**, No. 4, p. 113.

Cleve, H. (1958). *Z. Rheumaforsch.*, **17**, 350.

—— and Hartmann, F. (1957). *Klin. Wschr.*, **35**, 334.

Creyssel, R., Fine, J. M., and Morel, P. (1959). *Rev. Hémat.*, **14**, 238.

Fenrych, W., Jazienicki, B., Mackiewicz, S., Mackiewicz, U., and Twardowski, K. (1959). *Pol. Tyg. lek.*, **14**, 1937.

Francq, J., Eyquem, A., Podliachouk, L., and Jacqueline, F. (1959). *Ann. Inst. Pasteur*, **96**, 413.

Giedion, A., and Scheidegger, J. J. (1957). *Helv. paediat. Acta*, **12**, 241.

Grabar, P. (1960). *Triangel*, **4**, 185.

—— and Burtin, P. (1960). "L'analyse immuno-electrophorétique". Masson, Paris.

—— and Williams, C. A. (1953). *Biochim. biophys. Acta*, **10**, 193.

—— —— (1955). *Ibid.*, **17**, 67.

Hitzig, W. H. (1957). *Helv. paediat. Acta*, **12**, 596.

Mackiewicz, S., and Fenrych, W. (1959). *Postępy Hig. Med. dósw.*, **13**, 809.

McCluskey, R. T., Benacerraf, B., Potter, J. L., and Miller, F. (1960). *J. exp. Med.*, **111**, 181.

Ouchterlony, O. (1953). *Acta path. scand.*, **32**, 231.

Scheidegger, J. J. (1955). *Int. Arch. Allergy*, **7**, 103.

Schmid, K., and MacNair, M. B. (1956). *J. clin. Invest.*, **35**, 814.

Schultze, H., and Schwick, J. (1957). *Behringwerke Mitteilungen*, heft 33.

Analyse immuno-électrophorétique des protéines sériques

RÉSUMÉ

On procéda à l'analyse immuno-électrophorétique des sérums de 43 malades atteints d'arthrite rhumatismale et de 22 malades atteints de spondylarthrite ankylosante, des liquides synoviaux de 8 malades atteints d'arthrite rhumatismale et de l'urine de 2 malades atteints d'arthrite rhumatismale compliquée d'une maladie rénale.

Dans le sérum de beaucoup de cas d'arthrite rhumatismale et de spondylarthrite ankylosante on trouva des taux augmentés de glucoprotéine alfa-1 et alfa-2.

Le résultat le plus constant dans les deux groupes fut une augmentation de la beta-2 macroglobuline. Dans les sérums des cas d'arthrite rhumatismale et de spondylarthrite ankylosante on trouva un double arc de globuline gamma. On discute l'importance de ce résultat.

Les tableaux immuno-électrophorétiques du liquide synovial et de l'urine furent comparés à ceux offert par les sérums des mêmes malades.

Análisis imuno-electroforético de las proteinas séricas

SUMARIO

Se llevaron a cabo análisis imuno-electroforéticos en sueros procedentes de 43 enfermos con artritis reumatoide y 22 con espondilartritis anquilosante, en líquido sinovial de ocho enfermos con artritis reumatoide y en orina de dos enfermos con artritis reumatoide complicada con enfermedad renal.

En el suero de muchos de los enfermos con artritis reumatoide y espondilartritis anquilosante se encontró un aumento de la cantidad de alfa-1 y alfa-2 glucoproteinas.

El hallazgo mas constante en ambos grupos fué el aumento de beta-2 macroglobulina. En sueros de enfermos con artritis reumatoide y espondilartritis anquilosante se encontró un doble arco de gama globulina. Se discute el significado de dicho hallazgo.

Los cuadros imuno-electroforéticos del líquido sinovial y de la orina fueron comparados con los hallados en el suero de los mismos enfermos.

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TREATMENT OF RHEUMATOID ARTHRITIS BY INTRAMUSCULAR TRIAMCINOLONE ACETONIDE AND TRIAMCINOLONE DIACETATE

BY

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The results of a study (Zuckner, 1961) evaluating the therapeutic response of intra-articularly administered triamcinolone acetonide* (hereafter referred to as TActn) and triamcinolone diacetate* (TDac) suggested that large doses of these hormones had a profound systemic effect. The injection of either of these hormones in a dose of 100 mg. into a knee joint affected by rheumatoid arthritis resulted in a generalized anti-inflammatory response, including improvement in other inflamed joints as well as that injected. This generalized improvement usually persisted for 2 to 3 weeks. These favourable findings led to further study with these steroids, utilizing the more practical intramuscular route of administration.

Procedure

The acetonide and diacetate derivatives of triamcinolone were injected intramuscularly into 36 patients with rheumatoid arthritis. There were 112 injections, 68 of TActn and 44 of TDac. The dose per injection was 100 mg. These steroids were compared with hydrocortisone acetate (FAc) given by intramuscular injection in the same patients; there were seven injections of the 100 mg. dose of FAc, and eleven of 500 mg.

Patients were examined once a week at first in most instances, less often later. Subjective improvement in pain and stiffness and objective evidence of tenderness, heat, swelling, range of motion, capsular thickening, and fluid in involved articulations were determined and an estimated composite percentage recorded. These signs and symptoms were evaluated at each visit. The interval between injections was usually determined by the patient's subjective response, particularly the manifestation of pain. An effort was made to maintain at least 50 per cent. improvement as determined by the estimated composite figure. The triamcinolone steroids were administered in rotation for the most part.

Clinical evidence of toxicity was sought at each visit. Observations were made for moon facies, hirsutism, ecchymoses, blood pressure changes, body weight, oedema, and other possible alterations. Laboratory procedures included urine analyses, blood counts, and erythrocyte sedimentation rates (Westergren). These were performed at varying intervals, usually the day of an injection and one week later at the beginning of the study, and less frequently afterwards.

Other therapeutic measures were continued without modification with the exception of orally-administered steroids. 23 patients were receiving such medication when the study was instituted, and an additional three patients were taking steroids orally at other times during the study. In nineteen individuals the oral dose of steroid was lowered, and in ten of these it was completely discontinued. 28 patients were receiving gold salt therapy (gold sodium thiomalate or gold thioglucose); in eight of these individuals the gold was begun at the time of the first steroid injection. Twelve patients had already received more than 700 mg. gold salt before the first intramuscular injection of a triamcinolone derivative; in two others, the total dose of gold salt was between 500 and 600 mg. at the start of the study.

The duration of observation varied; seventeen patients were studied for 100 or more days, and six of these for approximately one year. The remaining nineteen patients were observed for an average of about 70 days each.

Results

The anti-inflammatory response to intramuscular injections of triamcinolone acetonide (TActn) and triamcinolone diacetate (TDac) was satisfactory in most patients. Improvement was considered satisfactory if there was at least 50 per cent. relief of the non-permanent clinical manifestations of the

* Supplied by Lederle Laboratories Division, American Cyanamid Company, Pearl River, New York.

disease for a period of 7 or more days after an injection. 83 per cent. of the patients showed such benefit at some time during treatment with TActn and 80 per cent. had similar results with TDac (Table I). When the results of individual injections were analysed, approximately 73 per cent. of injections with either TActn or TDac were followed by a satisfactory response. The average duration of improvement after an injection was 20·2 and 16·2 days for TActn and TDac respectively; the maximum period of relief after an injection was 69 and 75 days respectively. When these results were compared with those which followed the intramuscular injection of hydrocortisone acetate (FAc) in doses of 100 and 500 mg., the latter steroid proved inferior (Table I). The 100-mg. dose of FAc was almost completely ineffective by comparison, and the 500-mg. dose gave significantly poorer results. The average duration of improvement with the 500-mg. dose of FAc was 5·2 days, and six injections were followed either by no improvement or by not more than 3 days of benefit. The maximum period of relief was 17 days with this 500-mg. dose. The 100-mg. dose of FAc was followed by an average of 1·1 days of improvement.

TABLE I

RESULTS WITH INTRAMUSCULAR INJECTIONS OF TRIAMCINOLONE ACETONIDE (TActn), TRIAMCINOLONE DIACETATE (TDac), AND HYDROCORTISONE ACETATE (FAc) IN PATIENTS WITH RHEUMATOID ARTHRITIS

Drug		TActn	TDac	FAc	
Dose (mg.)		100	100	100	500
No. of Injections		68	44	7	11
Average Duration of Improvement (days)		20·2	16·2	1·1	5·2
Maximum Improvement (days)		69	75	5	17
Injections with Satisfactory Improvement	No.	50	32	0	4
	Per cent.	73·5	72·7	0	36

A comparison of the relative efficacy of the triamcinolone derivatives in individual cases was made in fourteen patients who received at least two injections each of TActn and TDac. Fewer injections in a patient were not satisfactory for evaluation because of the wide variability in improvement sometimes observed from one injection to the next. Thus, it was possible for one injection of either of the triamcinolone steroids to give very satisfactory results, and for this to be followed by a very poor response to the next injection of the same drug. Causative factors for this variability in response (such as an obvious change in the course of the disease or an increase in physical activity) were not apparent. In patients in whom suitable comparisons were made, ten derived greater benefit from TActn, and four had more improvement from TDac.

Patients receiving gold salts simultaneously with intramuscular steroid therapy were divided into two groups for analysis:

(1) Those who were either beginning gold salt therapy or who had received a total dose of less than 700 mg. when intramuscular steroid injections were started;

(2) Those who had a total dose greater than 700 mg. during the period of intramuscular hormone administration.

Four patients initially in the first group (less than 700 mg.) had received enough gold salt by the end of the study to fall into the second group (more than 700 mg. gold salt) making a total of sixteen patients in each group. This division into two groups was done to evaluate any possible effect of gold salts on the results. The separation at the 700-mg. total dose level was selected on the assumption that total doses greater than this would be less likely to influence the improvement attained from one injection of steroid to the next. There were 23 injections of TActn and fifteen injections of TDac in the group that received less than 700 mg. gold salt and these resulted in improvement after each intramuscular steroid injection averaging 23·4 and 15·9 days respectively. In the second group, there were 31 injections of TActn which resulted in an average duration of improvement after each injection of 19 days, and twenty injections of TDac, followed by improvement averaging 16·6 days. Simultaneous treatment with gold salts apparently had no significant effect on the results.

The average daily maintenance dose of orally administered steroids at the beginning of the study was equivalent to 7·5 mg. triamcinolone (free alcohol form, hereafter referred to as triamcinolone). Sixteen patients were receiving triamcinolone orally, three dexamethasone, two prednisone, and two 6-methyl prednisolone. Dosages of the latter steroids were converted to triamcinolone dosages for evaluation purposes, using the following dosage ratios:

$$\underset{4}{\text{triamcinolone}} : \underset{0.5}{\text{dexamethasone}} : \underset{5}{\text{prednisone}} : \underset{4}{\text{6-methyl prednisolone}}$$

At the end of the period of observation, the average daily maintenance dose was equivalent to 4 mg. triamcinolone.

The total daily steroid dose, that is, the daily oral maintenance dose plus the daily intramuscular dose (the latter obtained by dividing the dose of steroid injected intramuscularly by the days of satisfactory improvement) was determined at the end of the study and compared with the daily oral maintenance dose initially. To balance the doses of TActn and TDac, it was assumed that these steroids when given intramuscularly were equivalent mg. for mg. to the orally-administered free alcohol form of triamcinolone. Thus, of nineteen patients in whom an attempt was made to lower the oral steroid dose, there were ten in whom the total oral plus intramuscular dose daily at the end of the study was greater than the original oral dose daily; and in two the comparative doses for each period were equal. In seven patients the total oral plus intramuscular dose daily at the end of the period of observation was less than the daily oral dose at the beginning. These seven patients had a daily oral maintenance dose of triamcinolone initially of 7·3 mg. as compared with the combined oral plus intramuscular dose daily at the termination of the study of 4·5 mg.

The onset of improvement after the intramuscular administration of TActn and TDac was usually first noted on the morning after an injection. At times, patients described improvement beginning 3 to 5 hours after an injection, and less frequently, 48 hours after an injection. In some cases the improvement was gradual over a few days, but most often, maximum improvement developed by the day following the injection and then would persist as such for approximately 2 to 3 weeks.

Eleven patients showed marked subjective and objective improvement as compared with results from previous methods of therapy, including relatively much larger doses of steroids administered orally in some. One patient (A.R.A. Classification II, III: Steinbrocker, Traeger, and Batterman, 1949) has been free of objective evidence of synovitis and almost completely asymptomatic for a period of 70 days after only one injection of TActn, whereas, she previously had marked (3+) activity and synovitis continuously for 3 years before the injection.

The side-effects of TActn and TDac injected intramuscularly are recorded in Table II (opposite). Many of these are similar to those noted with orally administered steroids. Since 23 patients were taking steroids orally at some time during the study, it was difficult to evaluate hormonal reactions in these individuals as those due specifically to the intramuscular preparations. To overcome this difficulty, different categories are tabulated regarding the dose of steroid both before and during the study. It is noted that not all injections resulted in similar reactions in the same individual. Thus, only six out of twenty injections of TActn or TDac in four patients resulted in euphoria. In one of these individuals, the euphoria developed within 2 minutes after an injection and was associated with a "hot" feeling in the abdomen, suggesting possible entrance of the steroid into the systemic circulation at the time of injection. This reaction lasted 3 hours. Nine out of fifteen injections in four other patients resulted in a diuresis, usually beginning several hours after an injection and, at times, persisting for 3 to 4 days. When the period of anti-inflammatory improvement had run its course in these latter patients, those who had noted previous ankle oedema found that some swelling returned at the time of worsening, only to be relieved again by a subsequent intramuscular injection of TActn or TDac.

Marked weakness, nausea, and vomiting occurred in one individual about 10 days after each of two injections. These manifestations lasted 2 to 3 days and coincided with worsening of the joint findings after an initial 10-day period of improvement. Another patient described marked weakness, tiredness, and dyspnoea after each of three injections occurring simultaneously with the reappearance of increased synovitis following 10 days of satisfactory improvement. Two injections in this last patient were not followed by these symptoms. In each instance relief was obtained by another steroid injection. It was not possible to obtain biochemical proof of possible adrenal insufficiency in these cases. Electrolyte determinations of Na, K, and Cl performed at the time of one of the episodes of vomiting in the first individual gave normal results.

The features of moon facies, ecchymoses, and hirsutism are also tabulated. There were fewer ecchymoses in two patients and less moon facies in three as compared with the previous period of oral steroid therapy. In only one of three patients with less moon facies was the total daily dose of oral plus intramuscular steroid less than the daily dose of oral steroid originally.

Epigastric burning developed in one case; this did not occur previously while the patient was taking steroids by mouth. In another patient, there was less epigastric burning during the period of intramuscular steroid therapy; in this patient it was possible to lower the oral dose of dexamethasone, but the total daily dose of steroid was still greater than the previous oral dose alone. The lowering of the dexamethasone dose may have been responsible for the decreased gastrointestinal symptoms.

TABLE II

SIDE-EFFECTS OF INTRAMUSCULAR THERAPY WITH TActn AND TDac

Reactions		No. of Patients Affected	Patients on Oral Steroids	Total No. of Injections	Number of Injections followed by Reactions	Total Daily Dose of Oral plus Intramuscular Steroids Compared with Previous Oral Doses		
						Greater	Equal	Less
Euphoria		4	3	20	6	3	—	—
Diuresis		4	3	15	9	1	1	1
Muscle Cramps		2	2	9	2	1	—	1
Questionable Adrenal Insufficiency		2	0	7	5	—	—	—
Irritability and "Nervousness"		2	2	6	3	2	—	—
Severe Pain locally after an Injection		1	1	5	1	—	—	1
Flushes		1	0	3	1	—	—	—
Dizziness and Nausea shortly after an Injection		1	1	2	1	1	—	—
Abdomen "Hot", and Euphoria shortly after an Injection		1	0	5	1	—	—	—
Reaction to Oral plus Intramuscular Steroid Therapy combined as compared with Oral Steroid Therapy Alone								
Ecchymoses	More	1	1	2		1	—	—
	Same	9	9	27		6	2	1
	Fewer	2	2	7		—	—	2
Moon Facies	Greater	5	5	20		5	—	—
	Same	6	6	18		4	1	1
	Less	3	3	9		1	1	1
Hirsutism	More	1	1	7		1	—	—
	Same	2	2	8		1	—	1
Epigastric Burning	Greater	1	1	5		—	—	1
	Less	1	1	2		1	—	—
Appetite	Same	1	1	3		1	—	—
	Improved	1	1	5		—	—	1

Another patient had anorexia and lost 27 lb. while receiving oral triamcinolone in a maintenance dose of 8 mg. daily. During the period of intramuscular steroid therapy in this patient, no steroids were given orally; her desire for food returned, and she gained 7 lb. over a 3-month period.

Coincident with improvement was a decrease in the erythrocyte sedimentation rate in most patients tested. When the beneficial effects of the hormone were no longer present, the sedimentation rate usually rose again in conjunction with clinical worsening. Leucocytosis also appeared after many injections. No glycosuria was detected. Blood pressure elevation was not encountered with one possible exception; this patient had a history of hypertension before the study, but had had only one recorded blood pressure as a control (132/88). Subsequent values during the next 6 months of intramuscular steroid therapy averaged about 200/116. During this interval she had seven intramuscular injections of TActn and TDac. In the past month reserpine and chlorothiazide have been administered, and the blood pressure has fallen to 160/110.

This intramuscular method of steroid administration was discontinued in nine patients for the following reasons: inadequate or no improvement—five; no further need for steroids—two; patient contact lost—two. Two of the five patients with unsatisfactory improvement had sufficient "irritability and nervousness" to also warrant the discontinuation of therapy.

Discussion

The aim of much research in the field of rheumatic diseases in the past several years has been to obtain steroids with greater anti-inflammatory action but with fewer side-effects. The most recent oral preparations, triamcinolone free alcohol (or triamcinolone), 6-methyl-prednisolone, and dexamethasone, offer certain advantages, but are associated with undesirable physiological reactions

similar in many respects to those of the originally introduced anti-rheumatic hormones. No oral preparation combining a good anti-inflammatory response with relatively minor toxicity is yet available. The possibility of administering steroids intramuscularly in an attempt to obtain a satisfactory response with fewer or less severe side-effects has been examined in this study. One investigator (West, 1958) has previously reported his experiences with intramuscular injections of prednisolone acetate in the treatment of rheumatoid arthritis. He administered the steroid at regular weekly intervals for periods of 16 to 45 weeks. His patients derived satisfactory improvement from this treatment, and, in some instances, had a decrease in gastric disturbances.

In this study 100-mg. doses of triamcinolone acetonide (TActn) and triamcinolone diacetate (TDac) gave marked systemic responses when injected intramuscularly. Relief of both subjective and objective rheumatic manifestations as regards pain, stiffness, range of motion, and degree of synovitis was very striking in the majority of instances with either of these preparations. The improvement usually persisted at a satisfactory level for 2 to 3 weeks after a single injection. The duration of improvement was usually greater following an injection of TActn than of TDac, the reverse being true significantly less often. Improvement from intramuscular injections of the triamcinolone derivatives was far greater than the benefit derived from intramuscular injections of hydrocortisone acetate (FAc) in 100- or 500-mg. doses.

In an attempt to explain the difference in response to these hormones, one might question the relative equality of the doses as used in this study. Was 100 mg. TActn equal to 100 mg. TDac? Were these latter doses equivalent to 500 mg. FAc? Triamcinolone and FAc when administered orally have an anti-inflammatory ratio of 5 : 1 when equal weights are compared; but there has been no evaluation of the relative effectiveness of these drugs when administered intramuscularly. The author has not found any description in the literature of the comparative efficacy of intramuscular doses of triamcinolone, TActn, and TDac. Preliminary studies (Zuckner, 1961) with the intra-articular administration of TActn and TDac revealed no significant difference in local anti-inflammatory response between the 20-mg. dose of TActn and the 25-mg. dose of TDac. However, the minimal effective dose of each preparation was not determined and, therefore, basic dose levels were not compared. Animal studies by Ringler, Bortle, Heyder, Monteforte, Perrine, and Ross (1959) indicated that TActn was 21 times as potent as hydrocortisone for liver glycogen deposition in rats when injected subcutaneously, and 167 times as potent as hydrocortisone when administered orally. Liver glycogen deposition was six times greater with subcutaneously administered triamcinolone than with hydrocortisone, and 42 times greater with oral administration than with hydrocortisone. These values for triamcinolone were lower than those previously reported by Perrine, Bortle, Heyder, Partridge, Ross, and Ringler (1959). When thymus involution in rats was studied by Ringler and others (1959), TActn injected subcutaneously was 29 times more potent than hydrocortisone, and 75 times more potent than hydrocortisone when both drugs were given orally. It is, therefore, possible that the different anti-rheumatic responses to the intramuscular injection of TActn, TDac, and FAc could be explained at least in part by inequalities of dosage since relative dosages have not been clearly evaluated. Other factors, however, have to be considered.

It is interesting to speculate on the significantly greater duration of improvement which followed intramuscular injections of the triamcinolone derivatives as compared with FAc. Is this greater improvement due to a depot effect of TActn and TDac, whereby the hormone is slowly released into the circulation over the period of sustained improvement? This suggested depot mechanism requires evaluation, but its substantiation may have to await the availability of isotopically labelled triamcinolone or, perhaps, an adequate method of measuring blood levels of triamcinolone in order to follow the absorption of the injected material. A partial answer may be derived by studying the blood levels of 17-hydroxycorticoids after an injection of TActn or TDac. One such experiment (Zuckner, 1961, unpublished) was performed in a rheumatoid patient after a 100-mg. intramuscular injection of TDac. This subject did not show an anti-inflammatory response to the injection. An initial suppression of the 17-hydroxycorticoid level in the blood was noted within 4 hours, with a subsequent return to normal values 7 days later. The adrenal cortex was evidently suppressed for approximately 7 days, but interpreting this in terms of absorption rates is hazardous.

Another possible explanation of the greater improvement with TActn and TDac might be related to the initial massive steroid dose employed. This would imply that a sudden high level of hormone in the blood would have a greater physiological effect than a prolonged lower level. This has proved to be a vital factor in certain

experimental conditions as, for example, in the production of Alloxan diabetes in rats (Lazarow, 1946; Gomori and Goldner, 1945). A sudden high blood level of the agent might cause a greater effect in cells that have a greater avidity for the material than in other cells in the body. The inflammatory cells in synovial tissue probably would have an increased permeability and so might absorb large molecules much more rapidly. In order to get enough steroid into inflamed cells, a high concentration for a short time might be more apt to overcome the cell wall barrier than a more prolonged lower level. Another consideration would be that, if the agent is inactivated rapidly, it must be able to act before inactivation occurs; higher blood levels would then be more likely to provide the opportunity for the action to take place than prolonged lower blood levels.

This intramuscular method of administering steroids, in particular TActn and TDac, offered certain advantages and partially satisfied the criteria for a more effective anti-inflammatory drug. In approximately 25 per cent. of the patients the disease was controlled on a smaller daily maintenance intramuscular dose of steroid than that given orally before this study. Six individuals who had taken steroids orally for prolonged periods had better and more sustained relief from the intramuscular injections of TActn and TDac, and were maintained on this latter therapy alone. In eight others, the combination of oral and intramuscular steroid therapy proved more beneficial than the oral medication by itself; the oral dose in these patients was gradually decreased, but was supplemented by occasional intramuscular injections of TActn or TDac. Nine patients who had never taken steroids previously were adequately controlled by intramuscular injections of TActn and TDac. Toxicity was generally the same as that seen with previous hormone therapy. In two patients there were fewer ecchymoses and, in three, less moon facies during the period of parenteral therapy. Those who developed a greater degree of moon facies and more ecchymoses while on the study were receiving relatively larger daily doses of steroid and would, therefore, have been expected to show more of these changes. Euphoria was the only complication in slight excess as compared with the previous control period of oral steroid medication, but this was not severe enough to require discontinuation of treatment. The period of observation was not sufficiently long to study other reactions associated with steroid therapy, such as osteoporosis and peptic ulceration. Further evaluation will be necessary to determine the true incidence of toxicity. These preliminary findings suggest that fewer side-effects occur in some cases with this intramuscular method of administration than with oral administration.

Summary

Triamcinolone acetonide (TActn) and triamcinolone diacetate (TDac) were injected intramuscularly in 100-mg. doses into 36 patients with rheumatoid arthritis. There were 68 injections of the acetonide derivative and 44 of the diacetate. Satisfactory improvement lasted an average of 20·2 days after an injection of triamcinolone acetonide and 16·2 days after an injection of triamcinolone diacetate. The results from this form of treatment compared very favourably with those from previous oral steroid administration, and in approximately 25 per cent of cases was more satisfactory. Undesirable side-effects were possibly slightly diminished, but a further long-term study would be required for final evaluation.

REFERENCES

Gomori, G., and Goldner, M. G. (1945). *Proc. Soc. exp. Biol.* (*N.Y.*), **58**, 232.

Lazarow, A. (1946). *Ibid.*, **61**, 441.

Perrine, J. W., Bortle, L., Heyder, E., Partridge, R., Ross, E. K., and Ringler, I. (1959). *Endocrinology*, **64**, 437.

Ringler, I., Bortle, L., Heyder, E., Monteforte, A., Perrine, J. W., and Ross, E. K. (1959). *Proc. Soc. exp. Biol.* (*N.Y.*), **102**, 628.

Steinbrocker, O., Traeger, C. H., and Batterman, R. C. (1949). *J. Amer. med. Ass.*, **140**, 659.

West, H. F. (1958). *Ann. rheum. Dis.*, **17**, 273.

Zuckner, J. (1961). Unpublished observations.

Traitement de l'arthrite rhumatismale par des injections intramusculaires d'acétonide de triamcinolone et de diacétate de triamcinolone

RÉSUMÉ

On administra par voie intramusculaire l'acétonide de triamcinolone (TActn) et diacétate de triamcinolone (TDac) en doses de 100 mg. à 36 malades atteints d'arthrite rhumatismale. En tout, on donna 68 injections du dérivé acétonide et 44 injections du dérivé diacétate. Une amélioration satisfaisante persista en moyenne pendant 20,2 jours après l'injection d'acétonide de triamcinolone et pendant 16,2 jours après l'injection de diacétate de triamcinolone. Les résultats de cette forme de traitement ne le cédent en rien à ceux obtenus auparavant par l'administration orale des stéroïdes, et dans 25 pour cent des cas ils furent plus satisfaisants. Les effets secondaires furent peut-être moins accusés, mais des recherches ultérieures seraient nécessaires pour une évaluation finale.

Tratamiento de la artritis reumatoide por administración intramuscular de acetonido de triamcinolona y de diacetato de triamcinolona

SUMARIO

Se administraron intramuscularmente acetonido de triamcinolona (TActn) y diacetato de triamcinolona (TDac) a dosis de 100 mg. a 36 enfermos con artritis reumatoide. Fueron practicadas 68 inyecciones de derivado acetonido y 44 del diacetato. La satisfactoria mejoría perduró un termino medio de 20,2 días después de la inyección de acetónido de triamcinolona y 16,2 días después de la de diacetato de triamcinolona. Los resultados de esta forma de tratamiento no fueron inferiores a los obtenidos anteriormente por administration oral de esteroides, y en un 25% de los casos fueron más satisfactorios. Efectos colaterales indeseables fueron quizás algo menores, pero para una valoración final son necesarios estudios ulteriores a largo plazo.

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SIMPLE DETERMINATION OF THE L.E. FACTOR

LOOSE BODY TEST AND NUCLEUS AGGLUTINATION INHIBITION TEST

BY

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The diagnosis of systemic lupus erythematosus is based on the four following points:

(1) *The Clinical Picture.*—This does not always present itself in the complete classic form, as described by Osler (1895). The incomplete picture is difficult to recognize, and may appear as lupus arthritis, lupus nephritis, lupus hepatitis, and lupus thrombocytopenia.

(2) *The L.E. Cell Test.*—In about 80 per cent. of the proved cases the Hargraves test is positive. A theoretical objection to this test is that it employs phagocytosis which is a secondary reaction *in vitro* as indicator. The fixation of the specific L.E. gamma globulin to nuclei, which constitutes the first phase of the L.E. cell formation and results in loose body formation (Aisenberg, 1959; Rifkind and Godman, 1957; Rohn and Bond, 1952; Robineaux, Buffé, and Kourilsky, 1956), is not considered sufficient proof, but it is accepted that in some cases phagocytosis cannot occur because S.L.E. serum inhibits phagocytosis (Finch and Detre, 1958), has a lowered complement content in the active phase, and may show anti-complementary activity (Formijne and van Soeren, 1958).

The practical disadvantages of the L.E. cell test are its laboriousness and the reading-off difficulties in weakly-positive cases.

(3) *S.L.E. Serology.*—Some of the disadvantages of the L.E. cell test have been discounted by serological methods using the reaction between the nuclear components and the L.E. factor. The attention is directed to secondary indicators such as complement fixation, antiglobulin fixation, and nucleoprotein-latex precipitation. Only the anti-globulin fixation methods have proved to be sensitive enough (Miescher, 1955; Friou, 1958a, b, c; van Loghem, van der Hart, Hijmans, and Schuit, 1958; Engelfriet, van der Hart, and van Loghem, 1959). The antiglobulin-fixation test of Friou offers the best possibilities, as it is also suitable for quantitative use.

The intricate techniques required for the serological methods are a handicap for general use.

(4) *The Pathological-anatomical Picture.*—The histological picture of S.L.E. is typical and is characterized by haematoxylin staining bodies, fibrinoid necrosis, wire-loop lesions in the renal glomeruli, and onion-skin structures in the splenic arterioles, that may be demonstrated by biopsy. The most reliable criterion, the presence of haematoxylin staining bodies (Pollack, 1959; Worthington, Baggenstoss, and Hargraves, 1959), may, however, be overlooked if one omits to study the histological sections with a higher magnification (600-800×).

In practice the diagnosis of S.L.E. is sometimes not established for several years, or comes as a surprise finding at autopsy.

There is therefore still a need for a reliable simple quantitative method of determination that meets these difficulties. We believe to have found this in the two combined methods described below:

A. *Loose Body Test* (*L.B.T.*).—This microscopic method is based on the direct reaction between L.E.-factor and free leucocyte nuclei and is suitable for quantitative use (van Soeren, 1960).

B. *Nucleus-Agglutination Inhibition Test* (*N.A.I.T.*).—This test is based on the fact that free leucocyte nuclei suspended in "normal" serum, form a nucleoprotein clot. The reaction does not occur if all free leucocyte nuclei are loaded with L.E.-factor. It is a macroscopic test, which can also be used quantitatively (van Soeren, 1960).

Loose Body Formation

Free leucocyte nuclei incubated in a strong S.L.E. serum, all become loaded with L.E. factor in less than a minute, and are transformed into entirely homogeneous loose bodies which are histochemically and morphologically identical to the haematoxylin staining bodies. They remain present in the serum in a homogeneous suspension and, after sedimen-

tation, can be smeared out as a homogeneous film on an object glass. Hundreds of them are seen per visual field with a low magnification (80×).

This reaction is remarkably little thermosensitive and runs its course within a minute at both 0° and 56° C.

On stepwise dilution of the L.E. serum with normal serum (1:2, 1:4, 1:8, 1:16, etc.), and incubation of such a dilution series with leucocyte nuclei suspension, entirely homogeneous and structureless loose bodies are found in the smears of the first dilutions. However, the loose bodies become gradually less homogeneous in the higher dilutions, and begin to assume a grid structure. We called this type the "rough type of loose body". These loose bodies can also be smeared out on an object glass, as a homogeneous film.

L.E. Serum	1:1	1:2	1:4	1:8	1:16	1:32	1:64
Smooth Loose Bodies	++	++	++	++	+	—	—
Rough Loose Bodies	—	—	—	+	++	++	—

Loose body formation only occurs if the test serum contains the L.E. factor. In the opposite case, a nucleoprotein clot formation is observed, and the nuclei of the leucocytes liquefy into a thready mass of nucleoprotein, no longer to be smeared out on an object glass. In a smear of normal serum incubated with leucocyte nuclei, only these liquefied nucleoprotein clots are found. These clots are also observed in the higher dilutions of an L.E. serum when not all nuclei can be loaded with L.E. factor.

The presence of these nucleoprotein clots is also macroscopically visible, and this has led us to the discovery of the macroscopic phenomenon of nucleus agglutination.

Nucleus Agglutination

Leucocyte nuclei, incubated for 10-30 minutes at 37° C. in normal serum, agglutinate by gentle shaking into a clearly visible nucleoprotein clot. This reaction is blocked at 0° C., is incomplete at 20° C., and takes its full course within 1 or 2 minutes at 56° C. If clot formation occurs on shaking, the initially opaque serum clarifies and becomes transparent. This reaction does not occur if the leucocyte nuclei have been loaded with L.E. factor beforehand. In this case there is an inhibition of the nuclear agglutination, and the suspension remains homogeneous and opaque on shaking.

The nucleus agglutination inhibition phenomenon can also be followed-up quantitatively if the S.L.E. serum is stepwise diluted with normal serum:

L.E. Serum	1:1	1:2	1:4	1:8	1:16	1:32
Nucleus Agglutination Inhibition ..	+	+	+	±	—	—

This phenomenon is directly related with the loose body formation; the rapid fixation of the L.E. factor prevents the rather slow formation of the nucleoprotein clots:

L.E. Serum	1:1	1:2	1:4	1:8	1:16	1:32
Nucleus Agglutination Inhibition ..	+	+	+	±	—	—
Loose Body Formation	++	++	++	++	+	—

In the smear preparations of dilution 1:16, the nucleoprotein clots and the rough type loose bodies are visible beside each other.

Technique of the Loose Body and Nucleus Agglutination Inhibition Tests

A typical series of results is shown in Fig. 1 (opposite).

Material and Methods

(*a*) *Leucocyte Nuclei Suspension.*—The leucocytes are gained from heparinized blood of patients with a high erythrocyte sedimentation rate (more than 80 mm./hr). 30 ml. heparinized blood is set aside for 30 minutes under an angle of 60°. The plasma layer that contains the leucocytes is pipetted off, centrifuged (1,500 r.p.m.), and eluted three times with a sterile buffer solution of the following composition (Aisenberg, 1959):

8 g. NaCl
1·38 g. NaH_2PO_4
1 litre distilled water
Adjusted at pH = 7·0 with NaOH

The re-sedimented leucocytes are then shaken for 5 minutes with sterile distilled water in a 5 per cent. concentration, again centrifuged (1,500 r.p.m.), and transferred to a sterile buffer solution in a concentration of 10 vol. per cent. Provided it is prepared under sterile conditions and stored at

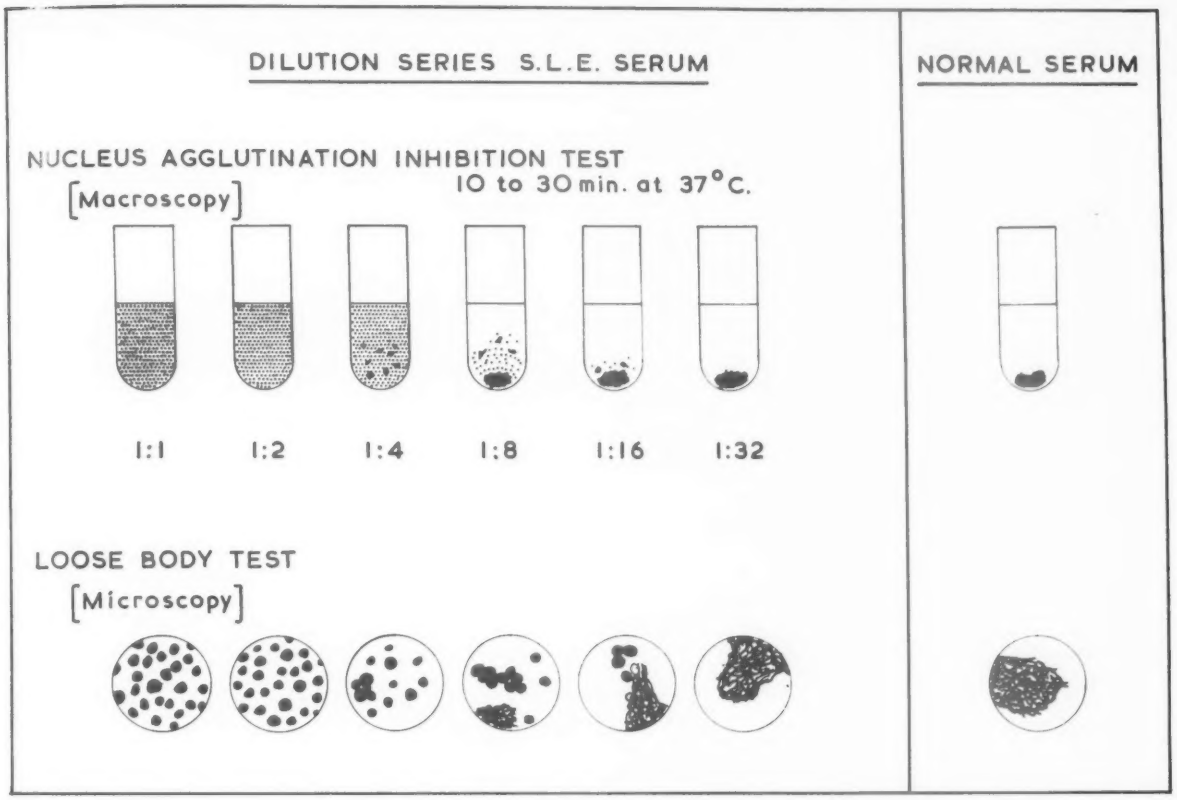

Fig. 1.—A typical series of results.

4° C., such a nuclear suspension is tenable for some weeks.

(*b*) *Method of Incubation* (*L.B.T. and N.A.I.T.*).—20 drops of the serum under investigation are thoroughly mixed with 3 drops of nuclear suspension and incubated for 30 minutes at 37° C. in a sterile agglutination tube (8 × 80 mm.).

(*c*) *Quantitative Determination.*—20 drops of normal serum are pipetted into 20 drops of L.E. serum. After thorough mixing, 20 drops of the mixture are transferred to a next tube, to which again 20 drops of normal serum are added. The process is repeated after thorough mixing. Thus a series 1:1, 1:2, 1:4, 1:8, etc., is obtained. From the last tube, 20 drops are thrown away. 3 drops of nuclear suspension are added to all tubes; the incubation is done as described under (*b*).

(*d*) *Combination with the L.E. Cell Test.*—An L.E. cell test can be carried out in a simple way parallel with the test described above. For this purpose, 1 drop of nuclear suspension and 3 drops of leucocyte suspension are added to 20 drops of serum; the incubation is likewise done for 30 minutes at 37° C.

(*e*) *Reading Off.*—In the first place the nucleus agglutination is read off. When the tube is carefully shaken between thumb and index finger, a macroscopically visible nucleoprotein clot is formed within about 10 seconds. This phenomenon does not arise in S.L.E. sera that contain sufficient L.E. factor.

The tubes are then centrifuged at 3,000 r.p.m. The sediment is smeared out on an object glass. dried, stained, and judged as a normal blood preparation.

Evaluation

The nucleus agglutination inhibition is only called positive if no trace of nucleoprotein clot formation is visible to the naked eye. Formation of strings on shaking, therefore, already indicates nucleus agglutination. The evaluation of the microscopical preparations is very simple.

The loose body formation is such a massive phenomenon—thousands of loose bodies are found in a single preparation—that even with a low magnification (80×) the preparation is recognized as positive.

Study with a high magnification (800×) is only necessary to judge the degree of homogenization of the loose bodies.

The negative preparations are also recognizable at once from the almost empty visual field and the appearance of nucleoprotein clots.

Between the two there is a small group of sera showing nucleus agglutination, in which a careful search of the microscopic preparation reveals some 20 to 100 rough loose bodies. These sera are recorded as sporadically positive. The same picture is found in the borderline titre of a dilution series of a positive serum. The highest dilution with massive loose body formation is, however, here accepted as the limit.

Results

Both methods were tested in 800 sera, 720 obtained at the Wilhelmina Hospital of Amsterdam by means of a circular letter asking for material from patients with a number of the syndromes which may include systemic lupus erythematosus. and eighty from normal subjects. The diagnosis is set out in Table I.

The highest titres obtained in the various conditions tested are shown in Table II.

TABLE II

HIGHEST TITRES OBTAINED WITH VARIOUS DIAGNOSES

Test	Diagnosis	Highest Titres Obtained
Loose Body	Systemic lupus erythematosus	1 : 128
	Rheumatoid arthritis	1 : 8
	Rheumatic fever	1 : 8
	Hydralazine syndrome	1 : 4
	Discoid lupus erythematosus	1 : 1
	Malignant hypertension	1 : 1
	Scleroderma	Sporadically positive
	Pleurisy	Sporadically positive
	Idiopathic thrombopenia	Sporadically positive
	Hepatitis	Sporadically positive
	False positive reaction (? syphilis)	Sporadically positive
	Chlorpromazine jaundice	Sporadically positive
	Hashimoto's struma	Sporadically positive
	Thrombosis of the central retinal vein	Sporadically positive
Nucleus Agglutination Inhibition	Systemic lupus erythematosus	1 : 64
	Rheumatoid arthritis	1 : 4
	Rheumatic fever	1 : 4
	Hydralazine syndrome	1 : 4

In one year the presence of the L.E. factor was traced in nineteen patients with the aid of the L.B. test and N.A.I.test. The patients, who had been admitted with varying syndromes, are listed in Table III (opposite).

Case 10 in Table II is described in detail as an example.

TABLE I

RESULTS OF TESTS IN 800 PATIENTS

Diagnosis	No. of Cases	Tests			
		Loose Body	Nuclear Agglutination Inhibition	L.E. Cell	Antiglobulin Fixation
Systemic Lupus Erythematosus	35	34	25	23	11 (of 21)
Rheumatoid Arthritis	208	28	17	10	1 (of 7)
Hydralazine Syndrome	2	2	2	2	0 (of 1)
Rheumatic Fever	22	4	1	—	Unknown
Discoid Lupus Erythematosus	13	4	—	—	Unknown
Malignant Hypertension	7	1	—	—	Unknown
Pleurisy	25	2	—	—	Unknown
Idiopathic Thrombopenia	12	4	—	—	Unknown
Hepatitis	36	1	—	—	Unknown
False Positive Syphilis Reaction	9	1	—	—	Unknown
Scleroderma	3	1	—	—	Unknown
Chlorpromazine-jaundice	3	1	—	—	Unknown
Hashimoto's Struma	1	1	—	—	Unknown
Thrombosis of the Central Retinal Vein	1	1	—	—	Unknown
Other Diagnosis	343	—	—	—	Unknown
Normal Subjects	80	—	—	—	Unknown
Total	800	85	45	35	12 (of 29)

* The Antiglobulin Fixation Test was carried out in the Central Laboratory of the Blood Transfusion Service (Director: Prof. J. J. van Loghem, M.D.).

TABLE III

CLINICAL PICTURE AND DIAGNOSTIC TESTS IN NINETEEN PATIENTS

Case No.	Sex	Age (yrs)	Clinical Manifestations	Tests			
				Loose Body	Nucleus Agglutination Inhibition	L.E. Cell	Antiglobulin Fixation
1	F	83	Arthralgia Hepatomegaly; Acute abdominal symptoms	1 : 2	1 : 1	—	—
2	F	39	Rheumatoid arthritis Pleurisy; Pericarditis; Hepatomegaly; Acute abdominal symptoms	1 : 4	1 : 1	weakly +	—
3	F	65	Pneumonia; Pleurisy; Pericarditis; Microscopic haematuria; Acute abdominal symptoms	1 : 8	1 : 4	+	+
4	F	38	Rheumatoid arthritis; Mitral stenosis; Hepatosplenomegaly; Microscopic haematuria; Leucopenia	1 : 8	1 : 2	—	—
5	F	64	Rheumatoid arthritis; Larynx arthritis; Iridocyclitis; Mitral stenosis; Hepatomegaly; Psychosis; Microscopic haematuria	1 : 2	1 : 1	—	—
6	F	65	Rheumatoid arthritis Iridocyclitis Psychosis Microscopic haematuria	1 : 1	1 : 1	—	—
7	F	57	Arthralgia Chronic hepatitis False positive serological test for syphilis	1 : 16	1 : 4	+	—
8	F	13	Acute hepatitis	1 : 16	1 : 8	+	+
9	F	16	Malignant hypertension Raynaud's syndrome False positive Wassermann reaction Thrombopenia Microscopic haematuria	1 : 1	—	—	—
10	M	59	Rheumatoid arthritis Migratory pneumonia	1 : 128	1 : 32	+	+
11	M	57	Glomerulonephritis Hepatomegaly Bilateral pulmonary fibrosis Macroscopic haematuria	1 : 2	—	—	—
12	M	43	Arthralgia Migratory exanthema Pneumonia Haemolytic anaemia Leucopenia False positive Wassermann reaction Microscopic haematuria	1 : 4	1 : 1	+	+
13	F	69	Liver cirrhosis Microscopic haematuria	1 : 1	—	—	—
14	F	67	Arthralgia Chronic hepatitis (1938) False positive Wassermann reaction	1 : 8	1 : 2	+	—
15	M	58	Rheumatoid arthritis Pleurisy Myocarditis	1 : 128	1 : 64	+	+
16	F	32	Polyarthritis Rheumatic fever	1 : 8	1 : 4	—	—
17	F	32	Pericarditis sicca	1 : 2	1 : 1	+	—
18	F	51	Rheumatoid arthritis Hepatitis Bilateral pleurisy	1 : 16	1 : 8	+	+
19	F	67	Hydralazine therapy (6 mths, 150 mg. per day) Myalgia Bilateral pneumonia Hepatomegaly	1 : 2	1 : 1	+	—

Case 10, a 59-year-old clerk, fell ill in November, 1959, with fever and joint complaints. In the middle of March, 1960, he developed a left-sided pneumonia, which spread to the right side a month later. In 1950 he had had a skin affection on the nose and cheeks.

Examination.—In the Out-patient Clinic the diagnosis of systemic lupus erythematosus was established and the patient was admitted to hospital. Infiltrations were found in both lungs, and the joints were painful on pressure, but did not show any objective abnormalities.

Laboratory Findings.—Hb 11·4 g. per cent.; erythrocytes 4·3 mill.; thrombocytes 400,000/c.mm.; leucocytes 4,600/c.mm.

Normal differentiation.

Erythrocyte Sedimentation Rate: 69 mm. hr.

Thymol Turbidity Test: 12 U.

Bromsulphalein Retention: 18 per cent. after 45 minutes.

Urine: no abnormalities.

Creatinine Clearance: 145 ml. per min.

Protein Spectrum: total protein: 64·7 g./mill., albumin: 20·5 g./mill., alpha$_1$-globulin: 3·8 g./mill., alpha$_2$-globulin: 7·9 g./mill., beta-globulin: 5·9 g./mill., gamma-globulin: 26·6 g./mill.

Serum Glutamic Oxalacetic Transaminase: 32 U.

Hijmans van den Bergh Reaction direct: negative, total: 0·4 U.

Wassermann Reaction: negative.

Serological Tests for Syphilis: negative.

Loose Body Test: positive, 1:128.

Nucleus Agglutination Inhibition Test: positive, 1:32.

L.E. Cell Test: markedly positive.

Antiglobulin Fixation Test: markedly positive.

Result.—The patient was treated with 30 mg. prednisone per day, later with 25 mg. per day. The clinical manifestations (lung infiltrates and joint complaints) disappeared entirely, and the L.B.T. and N.A.I.T. fell to lower values, but still remained strongly positive (1:16 and 1:8 respectively, see Fig. 2). The patient was discharged with continuation of the prednisone therapy.

Discussion

In experiments on the phagocytosis phase of the L.E. cell formation (Formijne and van Soeren, 1958), we discovered the lability of the phagocytosis, and observed the stability and constancy of the first phase of the L.E. cell phenomenon, the loose body formation, remained in many changing circumstances.

A study of the literature showed that in the L.E. cell test insufficient conclusive power was attributed to the direct reaction between nuclear material and L.E.-factor. The serological methods are exactly aimed at this reaction, but meet with difficulties in finding the correct indicators. Pathological anatomy is most reliable criterion for the diagnosis of S.L.E.; the haematoxylin staining bodies, chemically and morphologically identical to the loose bodies and inclusion bodies of the L.E. cell pheno-

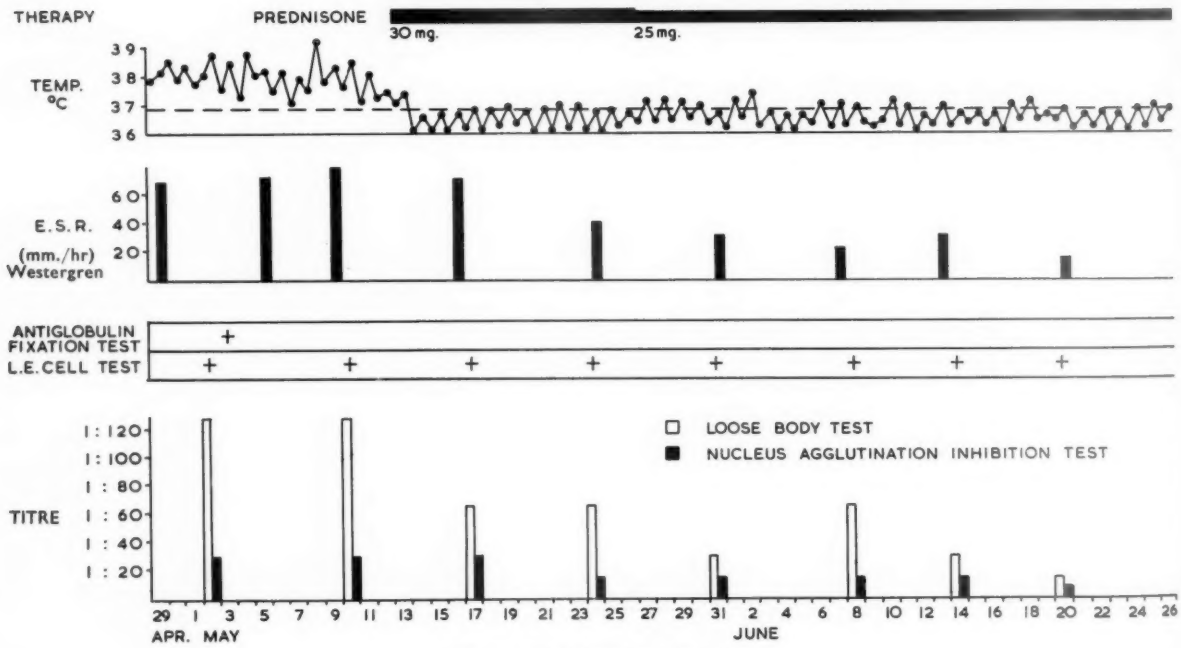

Fig. 2.—Clinical course of Case 10.

menon, are also the product of the direct reaction between L.E. factor and nuclear material. In the literature the loose body is not considered to be sufficiently definable, and it has even been stated that free nuclear material and S.L.E. serum cannot form loose bodies (Nathan and Snapper, 1958). This opinion is probably based on the fact that loose nuclei were used in which the free bonds of the nucleoprotein were already blocked in the process of liberating the nucleus from the cell. Another possibility is that this opinion was based on nuclear material of blasts or chick erythrocytes, which indeed, in our experience, do not give rise to a morphologically recognizable loose body formation and do not take part in the nucleoprotein formation.

The rough type loose bodies phenomenon that arises when the amount of L.E.-factor available per nucleus decreases, throws new light on the old controversy regarding the homogeneity of the inclusion body of the L.E. cell. Both van der Schoot (1959) and the present author are of the opinion that there are only quantitative and no qualitative differences.

The phenomenon of nucleus agglutination and its inhibition by serum containing L.E.-factor, which was discovered in our experiments, has already been known in a modified form. Tullis (1953) described nucleoprotein clot formation in old leucocytes, and Lee (1958) noticed that leucocyte agglutination inhibition is a property of S.L.E. sera of sufficient strength. Both authors point out that the leucocytes used for this reaction should be aged. It has appeared to us that the reaction proceeds much more quickly with leucocyte nuclei freed by distilled water. In the weekly titre checks of the L.B.T. and the N.A.I.T. we saw that even rest in bed can produce a fall in the titre. The administration of corticosteroids, however, does this more effectively and may abolish the phenomenon entirely, but the reaction may soon return after their withdrawal. The amount of L.E. factor demonstrable is not an absolute criterion of the severity of the disease process, but only an expression of the individual relationships in the patient.

Checking the titration is valuable in following up the spontaneous course of the disease and its therapeutic management.

The loose body test is reliable from titre 1:1 onwards (massive loose body formation in undiluted serum). The result: "sporadically positive" (20 to 100 rough type loose bodies) should be regarded with some reserve as long as no greater series of results is available.

The results with this test may throw some light on the clinical problems of systemic lupus erythematosus. It appears to be incorrect to persist in separating rheumatoid arthritis with a positive L.E.-cell phenomenon from systemic lupus erythematosus. In all but one of fourteen cases of L.E.-positive rheumatoid arthritis, which were clinically observed by us, abnormalities of liver, kidneys, heart, lungs, serous membranes, eyes, central nervous system, and so on, were demonstrable. These cases, all of which show a protracted course, may therefore be called cases of chronic lupus erythematosus disseminatus (Kurnick, 1956). This opinion is supported by the fact that in such cases the joint capsules and tendon sheaths may show a typical histological picture (Cruickshank, 1959).

The same objection can be advanced for lupoid hepatitis. According to our experience, liver function disturbances (bromsulphalein retention) and hepatomegaly are very frequent manifestations of systemic lupus erythematosus, and the literature shows that, in lupoid hepatitis, symptoms other than the L.E. cell phenomenon are the rule (Mackay, Taft, and Cowling, 1959; Taft, Mackay, and Cowling, 1960; Holman, 1960; Holman and Tomasi, 1960). The constant hypergammaglobulinaemia demonstrated in these cases, which gives rise to anti-complementary syphilis reactions, may also explain the weakly positive or absent L.E. cell phenomenon, since gamma globulin can have a strong anti-complementary activity and may therefore inhibit the phagocytosis. It is in these cases that the discrepancy between the L.E. cell test and the height of the loose body titre is most striking. Lupoid hepatitis thus appears to be a particular form of systemic lupus erythematosus, and lupus hepatitis would therefore be a better name for the condition.

Finally, there are strong indications of the dynamic nature of the anatomical abnormalities in systemic lupus erythematosus. The characteristic changes were not found on autopsy in two patients who had been treated for a long time with high doses of corticosteroids. This points to a continuous formation and breakdown of haematoxylin staining bodies, unless the reaction between antinuclear factor and nuclear material is blocked by high doses of corticosteroids. This is another reason for treating such patients continuously with corticosteroids (Dubois, 1960) to prevent the irreparable damage of the organs. which ultimately develops as a tissue reaction to the products of the anti-nuclear-factor-nucleus-complex.

Summary

Two simple qualitative and quantitative microscopic and macroscopic diagnostic methods (the *Loose Body Test* and the *Nucleus Agglutination*

Inhibition Test) are described. These tests are based on the direct reaction between the L.E. factor and free leucocyte nuclei.

As regards sensitivity, the two methods are superior to the L.E. cell test and the antiglobulin fixation test. The results of an investigation in 800 patients are reported, and the implications of the data obtained are considered.

REFERENCES

Aisenberg, A. C. (1959). *J. clin. Invest.*, **38**, 325.

Cruickshank, B. (1959). *Ann. rheum. Dis.*, **18**, 111.

Dubois, E. L. (1960). *J. Amer. med. Ass.*, **173**, 1633.

Engelfriet, C. P., Hart, M. van der, and Loghem, J. J. van (1959). *Vox Sang.* (*Basel*), **n.s. 4**, 485.

Finch, S. C. and Detre, K. D. (1958). *Clin. Res. Proc.*, **6**, 196.

Friou, G. J. (1958a). *Proc. Soc. exp. Biol.* (*N.Y.*), **97**, 738.

—— (1958b). *J. Immunol.*, **80**, 476.

—— (1958c). *Ann. intern. Med.*, **49**, 866.

Formijne, P., and Soeren, F. van (1958). *Lancet*, **2**, 1206.

Holman, H. (1960). *J. Pediat.*, **56**, 109.

—— and Tomasi, T. (1960). *Med. Clin. N. Amer.*, **44**, 633.

Kurnick, N. B. (1956). *Arch. intern. Med.*, **97**, 562.

Lee, S. L. (1958). *Blood*, **13**, 778.

Loghem, J. J. van, Hart, M. van der, Hijmans, W., and Schuit, H. R. E. (1958). *Vox Sang.* (*Basel*), **n.s. 3**, 203.

Mackay, I. R., Taft, L. I., and Cowling, D. C. (1959). *Lancet*, **1**, 65.

Miescher, P. (1955). *Vox Sang.* (*Basel*), **n.s. 5**, 116.

Nathan, D. J., and Snapper, I. (1958). *Blood*, **13**, 883.

Osler, W. (1895). *Amer. J. med. Sci.*, **110**, 629.

Pollack, A. D. (1959). *In* G. Baehr and P. Klemperer "Systemic Lupus Erythematosus", (Mount Sinai Hospital Monograph), p. 1. Grune and Stratton, New York.

Rifkind, R. A., and Godman, G. C. (1957). *J. exp. Med.*, **106**, 607.

Robineaux, R., Buffé, D., and Kourilsky, R. (1956). *Ann. Inst. Pasteur*, **91**, 109.

Rohn, R. J., and Bond, W. H. (1952). *Amer. J. Med.*, **12**, 422.

Schoot, J. B. van der (1959). Thesis, University of Amsterdam.

Soeren, F. van (1960). Thesis, University of Amsterdam.

Taft, L. I., Mackay, I. R., and Cowling, D. C. (1960). *Gastroenterology*, **38**, 563.

Tullis, J. L. (1953). "Blood Cells and Plasma Proteins." Academic Press, New York.

Worthington, J. W., Baggenstoss, A. H., and Hargraves, M. M. (1959). *Amer. J. Path.*, **35**, 955.

Procédés simples pour déterminer le facteur L.E.

RÉSUMÉ

On décrit deux procédés simples de diagnostic microscopique et macroscopique, qualitatif et quantitatif (Réaction du Corps Libre—*Loose Body Test*—et Réaction d'Inhibition de l'Agglutination du Noyau—*Nucleus Agglutination Inhibition Test*). Ces tests se basent sur une réaction directe entre le facteur L.E. et les noyaux leucocytaires libres.

La sensibilité de ces procédés est supérieure à la recherche des cellules L.E. et à la réaction de fixation de l'antiglobuline. On présente les résultats d'une étude chez 800 malades et on considère les implications des données obtenues.

Métodos simples para determinar el factor L.E.

SUMARIO

Se describen dos sencillos métodos de diagnóstico qualitativo y cuantitativo, microscópico y macroscópico (la Reacción del Cuerpo Libre—*Loose Body Test* y la Reacción de Inhibición de la Aglutinación del Núcleo—*Nucleus Agglutination Inhibition Test*). Dichas pruebas están basadas en la reacción directa entre el factor L.E. y núcleos leucocitarios libres.

La sensibilidad de estos métodos es superior a la busca de células L.E. y a la reacción de fijación de la antiglobulina. Se publican los resultados de una investigación en 800 enfermos y se consideran las implicaciones de los datos obtenidos.

Ann. rheum. Dis. (1961), **20**, 289.

AN UNUSUAL CLINICAL RECOVERY FROM SYSTEMIC LUPUS ERYTHEMATOSUS

BY

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This case is reported for two reasons. First, it illustrates that lupus nephropathy with renal failure and severe hypertension is not necessarily fatal, and that the hypertension may be reversible; secondly, the patient's unexpected recovery followed the menopause.

Case Report

A **housewife aged 51** came to hospital in July, 1955, complaining that for the previous 2 months she had suffered from attacks of pain in her right arm; these occurred principally at night, but were also provoked by peeling potatoes or carrying shopping. On direct questioning it appeared that for about 3 months she had not been completely well: her appetite had been poor and, contrary to her usual custom, she had been getting up at night to pass urine. Some 3 weeks previously she had had transient painful swelling of her right ankle, and for 1 week she had noticed a patchy non-irritating rash on her face and neck. She also mentioned that all her life her skin had tended to become blotchy after exposure to sunlight.

On examination she was febrile (99·8° F.). Her face and neck were covered by a symmetrical red scaling macular rash, sparing only the area around her eyes. Around the nail-folds of her fingers were red chilblain-like lesions. Her blood pressure ranged from 130 to 140/70 to 80. The urine contained 0·3 per cent. protein, with numerous red and white blood cells. *X* ray of the cervical spine showed clear evidence of disc degeneration, and this was presumed to have caused the pain which brought her to hospital.

Her erythrocyte sedimentation rate (Westergren) was at first 18 mm./1 hr, but within 2 weeks it had risen to 66 mm. Other tests showed: Hb 75 per cent., red blood cells 3·9 million/mm.^{3}, white blood cells 5,000/mm.^{3} (neutrophils 2,600/mm.^{3}). Blood urea 63 mg./100 ml. Plasma proteins 6·9 g./100 ml. (albumin 3·7, globulin 3·2). Paper electrophoresis: increase in gamma-2 globulin (14 per cent.). L.E. cells were seen in peripheral blood. A urine concentration test showed a maximum urinary specific gravity of 1·022. Chest *x* ray and intravenous pyelogram were normal.

A diagnosis was made of systemic lupus erythematosus (S.L.E.) with renal involvement, and treatment with cortisone was started on August 12, 1955. She was discharged from hospital 3 weeks later on 150 mg. cortisone daily. Her rash faded quickly, well-being and appetite improved, and the erythrocyte sedimentation rate fell to 14 mm./1 hr. Proteinuria and microscopic haematuria persisted.

On September 13, 1955, her blood pressure was found to be 180/105, and by November 22, 1955, it was 250/145. She was now re-admitted to hospital. Both optic discs were swollen, although there were no haemorrhages or exudates. Her face was moon-shaped, her complexion greasy, and her ankles oedematous. The blood urea had risen to 92 mg./100 ml.; the maximum urinary specific gravity after dehydration was 1·018, and the urea clearance values were 29 and 33 per cent. or normal.

Because of the oedema, cortisone was replaced by prednisone, stabilizing at 50 mg./day. The hypertension was moderately controlled by oral pentolinium tartrate. Her general condition gradually improved, the appearance of the optic discs became normal, and by June, 1956, the blood urea had fallen to 47 mg./100 ml. The dose of prednisone was reduced progressively. By February, 1957, the urine was free of protein, although it still contained granular casts and red and white blood cells.

During 1958 the patient's menses ceased, and during the next 2 years she was troubled by hot flushes and sweats.

In August, 1958, prednisone was withdrawn altogether. The patient, however, "felt awful", and complained much of muscle and joint pains. The blood pressure at the end of this 6-week steroid-free period was still 140/110, despite pentolinium. Prednisone 2·5 mg. daily was re-started, but 3 months later it proved possible to withdraw both steroid and hypotensive drugs.

The patient was seen regularly for a period of 18 months after therapy was stopped. After some initial fatiguability, she gradually regained a feeling of normal fitness and returned to full-time employment. Her blood pressure has averaged 140/87 (range 125 to 155/80 to 90). Her erythrocyte sedimentation rate has ranged from 10 to 15 mm./1 hr, and her blood urea from 42 to 49 mg./100 ml. The urine has usually been protein-free, though

a faint trace has been detected on occasion; the deposit has consistently revealed increased numbers of white blood cells and some granular casts.

Discussion

In their account of lupus nephritis, Muehrcke, Kark, Pirani, and Pollak (1957) noted that, in two patients with only mild renal injury, exacerbations of disease seemed to be associated with reversible hypertension; but in their experience severe hypertension, or hypertension associated with severe renal injury, was never reversed. Harvey, Shulman, Tumulty, Conley, and Schoenrich (1954), in their description of 138 cases of S.L.E., mentioned only one patient in whom the hypertension disappeared, and even then it had never been great, having ranged from 160 to 175/90 to 110. Recovery from severe hypertension does not seen to have been recorded hitherto in any case of S.L.E.

In the patient described here, the blood pressure level showed some correlation with steroid dosage; the pressure began to rise 1 month after treatment was started, and the highest pressures coincided with the highest doses. On the other hand the hypertension was also correlated with the severity of the nephritis, as judged by renal function and proteinuria. The relative importance of these two factors cannot be properly determined, but certain relevant observations may be stressed. First, malignant hypertension is an unlikely complication of steroid therapy *per se*; and similarly it is unlikely that the daily dose of 10 mg. prednisone given during the 3rd year could have been wholly responsible for diastolic pressures which—despite pentolinium—rose on occasion to 125 mm. Secondly, when at the end of the 3rd year steroid therapy was stopped, the diastolic pressure 6 weeks later was still 110 mm.—again despite pentolinium. For these reasons it seems likely that this patient's hypertension was due primarily to lupus nephritis, although it may have been aggravated by steroid treatment.

At one stage of her illness she had florid generalized disease, azotaemia, malignant hypertension, heavy proteinuria, and oedema. Her ultimate recovery is still not assured, and she has certainly suffered a measure of irreversible renal injury. But the fact that she is symptomatically a fit person leading a normal life indicates that the physician faced with such a case should not wholly despair nor pursue only half-hearted therapy.

This unusual recovery occurred at approximately the same time as the patient's menopause. A number of other observations also suggest that the female sex hormones may exert an unfavourable influence on the dissemination and course of this disease:

(1) Discoid lupus erythematosus shows only a slight female preponderance in incidence. Gold (1960) reported 105 cases of clinically uncomplicated discoid disease. After the exclusion of cases with a raised erythrocyte sedimentation rate, the female/male ratio in the remainder was only 1·3. Furthermore, there was no clear rise in this ratio during the female reproductive years: the ratio for the 3rd and 4th decades was the same as that for the rest of life.

The incidence of systemic lupus erythematosus, on the other hand, shows a heavy female preponderance. Table I combines the data from two large series, totalling together 212 cases (Harvey and others, 1954; and Medical Research Council, unpublished). There is a striking rise in the female/male ratio during the 3rd and 4th decades, although at all ages (except for the 1st decade) the ratio is higher than for discoid disease. A steadily progressive fall after the 3rd decade is interrupted by a rise in the 60+ age group. This may be a vagary due to small numbers; but there was a similar trend in a series of discoid cases reported by Gold (1960), among whom there were ten females aged 60 and over, but no males.

TABLE I

INCIDENCE OF SYSTEMIC LUPUS ERYTHEMATOSUS BY AGE (AT DIAGNOSIS) AND SEX, BASED ON COMBINED DATA OF HARVEY AND OTHERS (1954) AND THE MEDICAL RESEARCH COUNCIL (UNPUBLISHED)

Decade of Onset	Number of Cases		Female/Male Ratio
	Female	Male	
1	2	3	0·7
2	28	8	3·5
3	46	4	11·5
4	46	7	6·6
5	27	8	3·4
6	14	5	2·8
7+	13	1	13·0
Total ..	176	36	4·9

(2) It has been suggested by Soffer, Ludemann, and Brill (1955) and by Rupe and Nickel (1959) that systemic lupus erythematosus tends to be more severe among women than among men. There appear at present, however, to be no factual observations to confirm this suggestion.

(3) Some clinicians have formed the impression that, among females with the disease, mortality is higher during the reproductive years. Again, figures to support this contention do not seem to be

available. Merrell and Shulman (1955) estimated the prognosis in their series of cases of systemic lupus erythematosus, using a life table procedure. Their data may be used to form separate estimates of prognosis in women aged respectively under 45, or 45 and over, at diagnosis (Table II). The estimated survival rates at 2 years from diagnosis are not significantly different. (The true risk of dying from S.L.E. among the older group of women is probably less than appears in the Table, because of their relatively greater risk of dying from other causes.) It thus appears that a higher case fatality rate among younger women cannot at present be substantiated. On the other hand, Pollak (1961) has found that the risk of exacerbation of S.L.E. is very much greater during the first 8 weeks *post partum* than it is during pregnancy.

(4) Through the courtesy of the United States National Office of Vital Statistics, figures were made available for the numbers of deaths from lupus erythematosus in the United States, by age and sex, for the period 1956-58. In Table III these are presented as age-specific death rates. It can be seen that the male rate rises more or less steadily throughout life. At the extremes of life, the female rates are very similar to the male; but they are a great deal higher than the male rates for the quinquennia from 10-14 up to 50-54, and especially for the period between 20 and 49 years of age.

In order to obtain a more specific measure of the true mortality excess among females, one may deduct from the female rate at each age the corresponding male rate. (This procedure is based on the assumption that the changes in male rates with age represent a non-specific age effect which is likely to be common to both sexes.) The results are shown graphically in the Figure (overleaf), which also indicates the age-specific means for urinary oestrogen excretion, as determined by a study of 704 normal women by Pedersen-Bjergaard and Tønnesen (1948). The correspondence between the changes in excess female mortality from lupus erythematosus and the changes in oestrogen levels is quite close.

This remarkable mortality phenomenon is not shown by any other disease, apart from diseases of the female reproductive organs and the complications of pregnancy. The complete contrast between the age and sex patterns for systemic L.E. incidence and mortality on the one hand, and discoid L.E. incidence on the other, presents difficult but stimulating problems.

These observations favour, although they do not prove, the hypothesis that the female sex hormones tend to provoke or aggravate systemic lupus erythematosus. The evidence might be considered sufficient to justify the trial of androgen therapy or

TABLE III

DEATH RATES FOR LUPUS ERYTHEMATOSUS BY AGE AND SEX, UNITED STATES, ALL RACES, 1956-58

(FROM UNPUBLISHED DATA OF NATIONAL OFFICE OF VITAL STATISTICS)

Age (yrs)	Deaths per 10^6	
	Female	Male
<5	0·04	0·03
5–	0·30	0·18
10–	1·33	0·13
15–	2·79	0·61
20–	3·59	0·33
25–	2·66	0·48
30–	3·08	0·73
35–	3·86	0·40
40–	3·45	0·90
45–	3·60	1·03
50–	3·29	1·55
55–	2·34	1·96
60–	2·30	1·78
65–	1·83	2·02
70–	2·10	2·23
75 and Over	2·24	1·34

TABLE II

LIFE TABLES SHOWING PROBABILITY OF SURVIVING AMONG WOMEN WITH SYSTEMIC LUPUS ERYTHEMATOSUS, AGED UNDER 45 YEARS, AND 45 YEARS AND OVER

(DATA OF MERRELL AND SHULMAN, 1955)

Age (yrs)	Period from Diagnosis (mths)	No. of Cases				Probability of Dying in Period	Probability of Surviving	Cumulative Probability of Surviving
		Entering Period	Follow-up Terminated in Period	Dying in Period	At Risk, Estimated			
Under 45	0–	66	9	8	61·5	0·130	0·870	0·87
	6–	49	12	3	43	0·070	0·930	0·81
	12–	34	7	3	30·5	0·098	0·902	0·73
	18–23	24	6	1	21	0·048	0·952	0·69
45 and Over	0–	18	1	4	17·5	0·229	0·771	0·77
	6–	13	2	1	12	0·083	0·917	0·71
	12–	10	1	1	9·5	0·105	0·895	0·63
	18–23	8	3	0	6·5	0·000	1·000	0·63

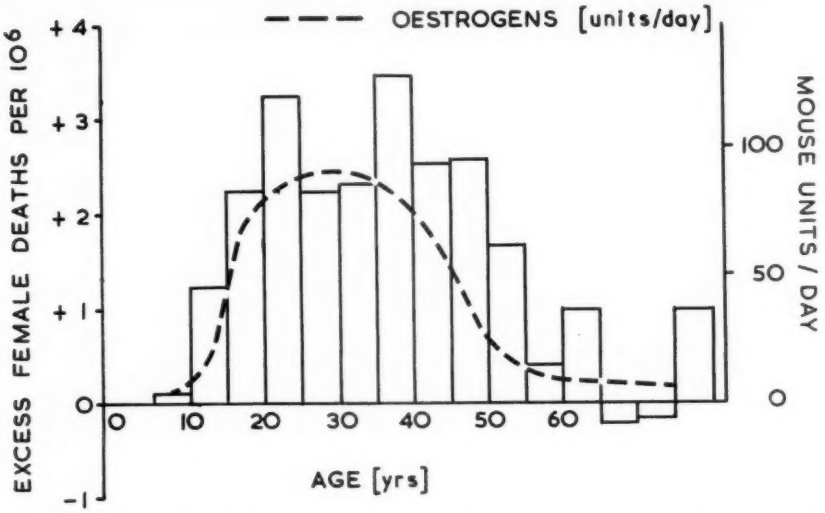

Figure.—(Female-male) death rates from lupus erythematosus, by age, United States, all races, 1956-58 (National Office of Vital Statistics, unpublished data) and mean oestrogen excretion rates, by age, in normal women (Pedersen-Bjergaard and Tønnesen, 1948).

(perhaps more appropriately) öophorectomy in menstruating women with severe S.L.E.—especially perhaps, in cases of lupus nephritis with azotaemia. It also indicates a need for detailed studies in individual patients on the relation between the activity of S.L.E. on the one hand, and pregnancy, menstruation, and hormone levels on the other.

Summary

(1) A case of systemic lupus erythematosus is reported in which severe nephritis was followed after 3 years of steroid therapy by reversal of azotaemia, hypertension, and proteinuria.

(2) This unusual recovery coincided approximately with the menopause. Statistical evidence related to sex differences in this disease is presented and found to be consistent with the view that the female sex hormones may exert an adverse effect.

I am grateful to Prof. W. S. Peart for permission to publish this case report, and to the Medical Research Council and the United States National Office of Vital Statistics for permission to use their unpublished data.

REFERENCES

Gold, S. (1960). *Brit. J. Derm.*, **72**, 231.

Harvey, A. M., Shulman, L. E., Tumulty, P. A., Conley, C. L., and Schoenrich, E. H. (1954). *Medicine (Baltimore)*, **33**, 291.

Merrell, M., and Shulman, L. E. (1955). *J. chron. Dis.*, **1**, 12.

Muehrcke, R. C., Kark, R. M., Pirani, C. L., and Pollak, V. E. (1957). *Medicine (Baltimore)*, **36**, 1.

Pedersen-Bjergaard, K., and Tønnesen, M. (1948). *Acta endocrinol. (Kbh.)*, **1**, 38.

Pollak, V. E. (1961). Personal communication.

Rupe, C. E., and Nickel, S. N. (1959). *J. Amer. med. Ass.*, **171**, 1055.

Soffer, L. J., Ludemann, W. H., and Brill, G. (1955). *Ann. N.Y. Acad. Sci.*, **61**, 418.

Cas peu fréquent de rétablissement de lupus érythémateux généralisé

Résumé

(1) On décrit un cas de lupus érythémateux accompagnée d'une néphrite grave qui fut suivie, après trois ans de thérapie stéroïde, par l'inversion de l'azotémie, de l'hypertension et de l'albuminurie.

(2) Ce rétablissement extraordinaire coïncidait à peu près avec la ménopause. On présente des données statistiques concernant le sexe dans cette maladie et on les trouve compatibles avec le point de vue que les hormones féminines peuvent y exercer un effet peu favorable.

Un caso poco frecuente de recuperación clínica de lupus eritematoso generalizado

Sumario

(1) Se describe un caso de lupus eritematoso, con nefritis grave, que fué seguida después de 3 años de terapéutica con esteroides por una reversión de la azotemia, hipertensión y proteinuria.

(2) Esta poco usual recuperación coincidió aproximadamente con la menopausia. Se presentan datos estadísticos de esta enfermedad con relación al sexo, que son compatibles con la hipótesis de que las hormonas sexuales femeninas pueden ejercer un efecto adverso.

Ann. Rheum. Dis. (1961), **20**, 293.

BOOK REVIEWS

Synovial Joints: Their Structure and Mechanics. By C. H. Barnett, D. V. Davies, and M. A. MacConaill. 1961. Pp. 304, 60 figs. Longmans Green, London. (50*s*.)

The authors set out to give a concise survey of modern views on articular function. At the outset let it be said that each of them has, in his own particular field, made a number of original contributions in one or more aspects of the structure or function of synovial joints.

The contents of the book are divided into the following sections: Section I deals with "The Components of Joints"; Section II deals with "The Biology of Joints"; Section III with "The Mechanics of Joints"; and Section IV with "The Functions of Joints".

An attempt has been made to answer a number of questions which, from time to time, have been raised on different aspects of joints. In answering some of these questions, the authors rightly point out that "Question leads to question, and the portal of knowledge is questioning". Nevertheless, a number of problems have been successfully answered by them. More problems are still unsolved, and the authors give an unbiased survey of the facts that are already known.

The book covers a wide scope and should be of value not only to the anatomist but also to the orthopaedic surgeon, the rheumatologist and the physiotherapist.

There is an extensive bibliography which gives a valuable guide to the more significant contributions, and should be of value to the intending research worker in this field.

The book can be recommended without reservation.

W. J. HAMILTON.

Le coude en pratique rhumatologique (The Elbow in Rheumatological Practice). By S. de Sèze and M. Maitre. 1960. Pp. 148, 105 figs. Masson, Paris. (34 NF.)

The presentation of this book is identical with that of "The Shoulder in Rheumatological Practice", also from the Viggo-Peterson Rheumatism Centre in Paris. Seemingly the authors have set themselves the task of covering the articular system with a series of monographs on individual joints. As before, the emphasis is on the illustrations which are excellently reproduced. All the main articular diseases which may affect the elbow, as well as a number of rarer bone diseases, are represented. This is, in fact, mainly a book of *x*-ray diagnosis of the elbow. If the series is to be completed it will form a useful documentation of joint lesions and could be helpful in teaching those unfamiliar with rheumatology. One cannot help wondering, however, if it will have that practical value in a rheumatological clinic, which is suggested by the title. It is mostly the severe examples of articular disease that are illustrated, and the illustrations are taken from patients in whom the diagnosis would be quite obvious from the clinical appearances elsewhere. On the other hand, careful clinical examination of the elbow may be very informative in early cases, particularly in elucidating problems of differential diagnosis, and it is just here that this book would be of little use. The tiny nodules of rheumatic fever, better seen than felt; the so-called "pre-nodular" thickening of elbow subcutaneous tissue; the rarer causes of lumps near the elbow, such as xanthomatosis and calcinosis; the skin lesions of psoriasis and disseminated lupus; the slight loss of full extension that may be the only sign of previous healed joint disease; the impacted fracture of the neck of the radius masquerading as arthritis; these are all examples of practical rheumatology which are not dealt with in this book. Nor do the authors give us much guidance on the practical problems of surgery and splinting of the elbow. No mention is made of the main neurological lesions resulting from damage to the soft tissue around the elbow joint, although ulnar paralysis due to bony enlargement is considered. This attractive book is not likely to be as useful as the title would suggest. ALLAN ST. J. DIXON.

The Biochemistry of Mucopolysaccharides of Connective Tissues, Biochemical Society Symposium, No. 20. 1961. Pp. 125. University Press, Cambridge. (15*s*.)

The symposia held from time to time by the Biochemical Society almost invariably prove of wide interest. That held in February, 1960, on the biochemistry of mucopolysaccharides of connective tissue must have been even more successful than usual as judged by this recently published report.

The structure and metabolism of the sulphated polysaccharides were clearly described by Helen Muir. Her contribution included an excellent account of the work on the chondroitin sulphate protein complexes and a useful summary of some relative variations with age and disease. The methods available for the histological demonstration of mucopolysaccharides in connective tissue were critically reviewed by R. C. Curran, and a brief communication by Sven Gardell of Stockholm described some of the recent technical advances for their isolation and identification. The structure and function of hyaluronate was then discussed by H. J. Rogers in an article that is a model of clarity and simplicity. Equally clear and valuable was Storey's brief description of the recently discovered role of the sugar nucleotides in the interconversion of sugars and in the synthesis of glucosides.

Kent's contribution on "some biochemical aspects of sulphated mucopolysaccharides" included much of the recent work on the mechanisms of sulphation as well as some useful references to other sulphated compounds of biochemical significance. The final paper by A. G. Walker on "the enzymic degradation of mucopolysaccharides" may well have proved somewhat indigestible at the end of such an intellectual feast and many will therefore welcome its publication so as to be able to digest it at leisure.

This small volume is a valuable contribution to the literature of its subject: it is accurate, up to date, and remarkably comprehensive. It can be recommended without reservation. L. E. GLYNN.

Ann. rheum. Dis. (1961), **20**, 294.

EMPIRE RHEUMATISM COUNCIL

TWENTY-FOURTH ANNUAL REPORT*

The 24th Annual Report was presented by the Chairman, Dr. W. S. C. Copeman, at the Annual Meeting held at the Hall of the Worshipful Society of Apothecaries on May 4, 1961.

Dr. Copeman began by stating that the year 1960 had been one of the most important in the history of the Council. In research the number of projects had risen from twenty in 1959 to thirty-two in 1960, and medical expenditure had reached a record sum of £56,800. The Council's Electron Microscopy Centre had been opened at St. Thomas's Hospital Medical School, a further Unit on the action of drugs had been established at King's College Hospital Medical School, and the first results of the work of the Field Survey Unit had been published.

In the sphere of education the bulletins issued periodically to all medical practitioners had received overwhelming approval and the Council's exhibit at the B.M.A. Scientific Exhibition had been judged to have the highest teaching value of all those exhibited. The financial support the Council had gained had also reached a new peak, led by three magnificent gifts from Mr. R. F. Macfarlane, and Sir Edward and Lady Lewis. The Council was no less grateful to all the thousands who had responded to the appeal made by Dr. Roger Bannister on television, which resulted in the amount of £11,400 being received.

Research

Field Survey Unit.—A very significant statement had recently appeared in the Annual Public Survey of the United States of America—"Rheumatism cripples in the largest number of cases and kills in the smallest. This very ability to cripple without killing now seems to put it in the lead of all other chronic diseases as of eminent social, economic and medical importance." This had been borne out by the first comprehensive population survey of its kind, which had shown the widespread prevalence of rheumatoid arthritis and other forms of rheumatism in Great Britain.

The survey, carried out by the Council's Field Survey Unit under the direction of Dr. J. S. Lawrence, had brought to light the fact that there were nearly 1½ million people suffering from rheumatoid arthritis in this country at any one time. Members of the medical profession had always suspected that more people suffered from this disease than was generally supposed, but even they had been startled by this figure. The survey had also shown that the changes caused by osteo-arthritis began to appear in about one person in ten by the age of 24 and rose steadily with age, until at 65 over 60 per cent. of all men and women had osteo-arthritis sufficiently acute to cause pain and disability, a total of 3¾ million people.

In producing these authoritative figures, the Field Unit had made an important contribution to knowledge. The survey had also revealed a hereditary tendency to certain forms of rheumatoid arthritis; that one person in twenty suffered from an acute form of rheumatism or polyarthritis which had not been previously recognized; and that disk degeneration affected nearly 20 million people over the age of 15. Dr. Lawrence and his team were to be congratulated on this significant contribution to knowledge.

Electron Microscopy Unit.—The Council's Electron Microscopy Centre at St. Thomas's Hospital Medical School had been officially opened by the Chairman of the National Research Fund Appeal, Col. the Lord Astor of Hever, on October 6. Work on osteo-arthritis had now begun under the direction of Professor D. V. Davies and the instrument was available for other research workers in the field of rheumatic diseases.

Industrial Rheumatism Unit.—This was based on Edinburgh University and began work during 1960.

Unit on Drug Action.—This has been endowed by the Council for a period of 5 years at King's College Hospital Medical School at a cost of £20,000, to study the action of drugs used in the treatment of rheumatic diseases.

Other Research.—During 1960 other research projects had been financed after careful scrutiny by the Scientific Committees, led by Professor G. A. Smart. These projects, covering a very wide field—rheumatoid arthritis, osteo-arthritis, the action of drugs, auto-immune factors, and many others—were spread throughout Great Britain—Edinburgh, Manchester, Sheffield, Birmingham,

* Full details of the activities of the Council for the year 1959-60 are given in the Report, which may be obtained from the Secretary, Mr. M. C. G. Andrews, Faraday House, 8 Charing Cross Road, London, W.C.2.

Cambridge, Bath, and London, being only a few of the places in Great Britain where research was going on.

One of the most important inquiries was being carried on at the University of Birmingham under Professor J. R. Squire. A sum of £200,000 had been raised among local industrialists to cover the cost of a special wing of the Queen Elizabeth Hospital, the building of which should be completed during 1962.

COMMONWEALTH

Sister organizations in Canada, Australia, and New Zealand were also continuing to increase their activities. The Australian Rheumatism Council's appeal for funds had received a magnificent start with the generous gift of £A100,000 from Mr. Spurway of Sydney.*

In conclusion the Chairman paid tribute to the many people who had made the work possible, especially Mr. Macfarlane and Sir Edward and Lady Lewis, and Lord Astor of Hever and other eminent industrialists who had brought the work of the Council to the notice of industry and thereby gained invaluable and growing support, and also to all the research workers at home and abroad.

For the work of the General Secretary, Mr. M. C. G. Andrews, and the Assistant Secretary, Brigadier Houchin, no praise could be too high. Without their hard and efficient work the progress would have been very much less striking. The loyal and efficient office staff was led by Mrs. V. Brown, whose retirement in the coming year would be a matter of much regret. Sir Richard Miller had been appointed regional representative for the North-West.

He also thanked the medical and lay members of the various working committees of the Council for their regular attandance at meetings throughout the year.

* The full report (p. 30) includes full details of the activities of these societies and of the research being carried out in the University of Otago, New Zealand, which is financed by the Council.

HEBERDEN SOCIETY

A joint meeting of the Ligue Française contre le Rhumatisme and the Heberden Society was held in Paris on May 27 and 28, 1961. At the Hôpital de la Pitié, Professor Layani, Director of the rheumatism service, welcomed the Heberden Society on behalf of the Ligue. After an inspection of the newly built unit, where the excellent facilities for out-patients and physiotherapy were greatly admired, papers were read from both Societies.

The Effect of Hemiplegia on the Development of Arthritis, by DR. MALCOLM THOMPSON (*Newcastle*) and PROF. E. G. L. BYWATERS (*London*): A review of the literature suggested that hemiplegia offered a protective mechanism against the development of arthritis, and further cases which supported this hypothesis were described. The first was a case of hemiplegia in which Heberden's nodes had developed only on the unaffected hand. Attention was drawn to the fact that there was only one report of a patient who had survived a hemiplegic episode in childhood and subsequently developed rheumatoid arthritis; case histories of three further patients were then presented. In all three there was similar protection against the development of rheumatoid lesions in the joints and subcutaneous nodule formation in the paretic limbs and there were striking differences in the radiological signs on the two sides. A brachial arteriogram in one of these patients showed arteritis to be present both on the side affected with rheumatoid arthritis and in the protected hemiplegic limb. Prof. Bywaters suggested that arteritis probably resulted from the circulating rheumatoid factor rather than the local presence of arthritis.

Resting the Cervical Spine, by DR. J. FORESTIER (*Aix-les-Bains*): The difficulties in trying to rest the cervical spine at night were described by Dr. Forestier. He then demonstrated the use of a cylindrical pillow with a restricted part in the centre which offered an adequate solution of this problem.

Studies with Radioactive Gold,* by DR. J. S. LAWRENCE (*Manchester*).

Temporary Loose Hip, by DR. G. CORDIER, DR. H. GARNIER, and DR. M. DARCY (*Paris*): The results were described of an operation for osteo-arthritis of the hip, the principle of which was section of the periarticular muscles in an attempt to overcome the painful muscular hypertonia in the region of the affected joint. More than one hundred cases had been operated on and 54 had been followed up for at least 6 months. Of these, 23 had had excellent results as regards pain and function, and 21 were good. Seven of these patients were demonstrated and their performance in walking with only a slight limp, bending, and even running was impressive. The actual technique of operation was shown in a film and the after-care, comprising traction for 15 days, followed by non-weight bearing physiotherapy for 5 months, was described.

Discussion.—The question was asked whether these results could have been obtained merely by taking the patient off weight-bearing for 3 months and employing a simple physiotherapeutic regime. This suggestion was

* To be published in full in the December, 1961, issue of the *Annals*.

repudiated by Prof. Coste, who said he had attempted to rest a number of such patients but had never seen results of this type after the use of conservative measures.

A Case of the so-called "Scandinavian" Form of Ankylosing Spondylitis, by DR. F. FRANÇON and DR. G. LEBLANC (*Aix-les-Bains*): The patient described was a 67-year-old mining engineer, who had developed his first symptoms of ankylosing spondylitis in 1943. There was spread to the cervical and lumbar spine and later to the shoulders and hips. The main treatment was physiotherapy and as he was unable to tolerate gold he received cuproxane. By 1947 the feet were involved and movement of the right hip had become restricted to 50 per cent. of normal. Although he had considerable stiffness he was able to lead a normal life for the next 10 years. In 1957 he was first noted to have swelling of metacarpophalangeal and proximal interphalangeal joints in the hands. The next year ulnar deviation was noted and about the same time the palmar aspects of the fingers and hands took on a purple erythema, which affected the whole hand but was particularly marked on the thenar and hypothenar eminences, and the skin became thin and wrinkled. *X* rays confirmed the severe involvement of the sacro-iliac joints, although complete ankylosis had not occurred by 1958 and radiographs of the hand showed a widespread erosive arthritis involving the wrists as well as the metacarpophalangeal and proximal interphalangeal joints.

A review of the literature seemed to show that, contrary to early ideas, the hands might be involved in ankylosing spondylitis; in 1955 Romanus found it in 27 of 117 cases of advanced ankylosing spondylitis. However, as far as the authors knew, theirs was the first case in which the purple erythema of the palms had been described. They had always felt that rheumatoid arthritis and ankylosing spondylitis were different entities, and on the basis of one case did not feel justified in suggesting that they were the same disease.

The Society was entertained to a lavish lunch at the Hôpital de la Pitié, and the meeting then moved to the Hôpital Cochin, where the afternoon session commenced with a tour of the newly-completed unit under the direction of Prof. Coste. Although this clinic is not yet fully occupied, the visitors were much impressed by the general layout and size, both of the clinical department, including the physiotherapy section, and the research laboratories.

Uricosuric Agents in Gout, by DR. G. D. KERSLEY (*Bath*): The efficacy and toxicity were described of four uricosuric agents (Benemid, Urelim, Anturan and Zoxazolamine) in fifty cases of gout followed over the past 3 years. Anturan 800 mg. daily had been found to be the most potent drug and the only complication seen was pain in the loin probably due to its potency. Urelim was found to be as effective as but less toxic than Benemid. Zoxazolamine 1·5 g. was of similar potency to 400 mg. Anturan. Aspirin inhibited the uricosuric action of all these agents, but paracetamol did not do so. During the first few weeks of uricosuric therapy there was a tendency to an exacerbation of acute symptoms with all four drugs, so that it was wise to cover this period with Colchicine. The importance of continuing uricosuric therapy, despite the return of serum uric acid to normal levels, was stressed.

Discussion.—DR. SIMON (*Montpellier*) described his experience with 150 cases and agreed that there was very little difference in the uricosuric effect of these drugs; if anything, he had been more impressed by Zoxazolamine. However, he had not been able to maintain low serum uric acid levels. Other workers reported that after long-term uricosuric therapy, uric acid clearance tests showed marked improvement.

DR. A. ST. J. DIXON (*London*), in a study of 35 patients, had found very little difference between the uricosuric agents, but on the whole he was tending to use higher doses of probenecid than Dr. Kersley and lower doses of Zoxazolamine, as he personally found Zoxazolamine the most toxic of the agents. He had noted individual variations in response and ended by commenting that, in a study of hyperuricaemia artificially produced by pyrazinamide, salicylate had been found more effective than these uricosuric agents in reducing the serum uric acid levels.

DR. J. H. GLYN (*London*) asked whether it was necessary to give Anturan several times a day; if so, it would probably rule itself out as a practicable method of long-term maintenance therapy.

DR. KERSLEY replied that it was premature to comment on this as work was still in progress.

Results of Varus Osteotomy in Hip Joint Dysplasia with or without Osteo-Arthritis, by PROF. R. MERLE D'AUBIGNÉ, DR. M. POSTEL, and DR. J. M. VAILIANT (*Paris*): The results of osteotomy in patients with hip joint dysplasia with partial subluxation, with and without secondary osteo-arthritis, were described. A total of 200 cases had been operated on over the last 7 years and 100 had had at least one year of follow-up. Of some 35 cases with partial subluxation of the hip, operated on before the onset of arthritis, 86 per cent. showed no pain at follow-up, practically all had retained similar range of movement, and 76 per cent. walked normally. Where osteo-arthritis had been present (79 cases), 85 per cent. had painless hips, but in seven cases pain had increased and had required further surgery. Radiological follow-up of this whole group showed improvement in the state of the osteo-arthritis in nineteen, no change in fifty, and slight aggravation in ten. It was concluded that osteotomy of the neck of the femur had given useful results in hip joint dysplasia, both prior to the onset of osteo-arthritis and when it was present.

Discussion.—The question of rest alone was again brought up, but it was felt that there was a mechanical advantage to be gained by surgery.

PROF. J. H. KELLGREN (*Manchester*) pointed out that the actual physiological effect of operation on the hip joint was not known; it was likely that for several weeks after surgery there was an increase in the turnover of collagen tissues.

Aseptic Osteo-necrosis of the Head of the Femur, by PROF. F. COSTE, DR. P. MASSIAS, and DR. N. CHATELIN (*Paris*): The cause of this osteo-necrosis had been investigated in fifty patients, of whom one-third gave a history of corticosteroid therapy. There was a frequent association with diseases inducing inflammatory vasculitis. Gout (in four cases), osteo-necrosis seen in other bones, familial incidence, and bilateral involvement, all suggested that some patients had a constitutional predisposition. Mechanical factors seemed to play only a secondary part. It was concluded that there were multiple aetiological agents but that a vascular abnormality could explain some of the various causes.

Attempt to evaluate the Use of an Anabolic Steroid during Maintenance Corticosteroid Therapy, by DR. H. COLENBRANDER (*Leiden*) and DR. BARBARA M. ANSELL (*Taplow*): This study was designed to see if the inclusion of an anabolic steroid in the therapeutic regime of patients, on maintenance corticosteroid therapy for various rheumatic diseases, would prevent or ameliorate spinal osteoporosis. 57 patients were divided into three age groups, 0-15, 16-40, and 41 years and over, and in each group half received 0·20-0·25 mg./kg. Dianabol for 8 weeks out of every 12, and this was repeated on three occasions unless contraindications arose. Clinical assessments were made at 3-monthly intervals, and lateral radiographs of the thoracic and lumbar spine (taken at week 0, 24, and 48 (± 2)) were used for assessment of osteoporosis by measuring the anterior border of the thoracic spine and also the lumbar spine score in adults. Postero-anterior radiographs of the hands (taken at week 0 and 48) were used primarily for assessing the rheumatoid process, and in juveniles, development. In all patients over the age of 16 there was no difference between the control and treated groups, and a further patient, treated similarly and studied intensively, showed increase in osteoporosis in iliac crest biopsies at week 48 and was still in a negative calcium balance at week 47. In the juveniles, both initially and throughout the trial, those in the control group were on high doses of corticosteroids and showed more crush fracture vertebrae. At the end of the period, further compressions had occurred in four patients in the control group and none in the treated group. However, side-effects were frequent, and these included deepening of the voice and severe facial and labial hirsutism in girls, as well as marked facial mooning and acne and suppression of menstruation often necessitating reducing the dose or stopping altogether. It was concluded that this was not a practical measure of controlling steroid osteoporosis.

Hyperparathyroidism, by DR. J. A. LIÈVRE (*Paris*): On the basis of 24 cases seen personally, the various clinical symptoms and radiological signs and laboratory findings, particularly phosphate clearance, were reviewed, together with various problems that might be encountered in reaching this diagnosis. It was emphasized that the patient might present with bone pain, gastric disturbances, renal symptoms, and generalized weakness, and in two cases in this series the psychological manifestations were the most outstanding presenting features. In some cases the diagnosis was obvious, but in others the radiographs showed great similarity to Paget's disease, carcinoma, and occasionally osteomalacia, while urolithiasis and ulcers were special problems. Clinical assessment and full investigation were sometimes unhelpful, so that the only way to make certain of the diagnosis was exploration of the neck.

After the scientific sessions, the Heberden Society was entertained to dinner at the Restaurant Renault at Puteaux. During the day the ladies had been looked after by the ladies of the French Rheumatology Society, presided over by Madame le Docteur Lièvre.

On Sunday, May 28, there was an expedition to Chantilly where it was possible to visit the lovely old castle, and this was followed by a delightful luncheon at Vieux Cèdre, in Plaily, the home of Dr. Sichère.

Dr. G. D. Kersley thanked the Ligue on behalf of the Heberden Society and particularly Dr. J. Forestier for all his care in planning this very successful joint meeting. Some 23 members of the Society were afterwards entertained at Aix-les-Bains.

NEW YORK RHEUMATISM ASSOCIATION

Officers, 1961-62

The following were elected to office at the Annual Meeting of the New York Rheumatism Association on April 18, 1961:

President:	Dr. Emmanuel Rudd
Vice-President:	Dr. Donald Mainland
Secretary-Treasurer:	Dr. Charles L. Christian

Ann rheum. Dis. (1961), **20**, 298.

OBITUARY

ANIBAL RUIZ MORENO, 1907-60

Professor Anibal Ruiz Moreno, M.D., professor of medical history in the medical faculty of the university of Buenos Aires and one of the leading rheumatologists in the Argentine, died suddenly on December 22, 1960, at the age of 54, while lecturing to his students.

He had worked in the department of medical history for 25 years, and had been director of the rheumatology department for over 20 years.

He was founder and president of the Argentine League against Rheumatism, president of the Pan-American League, and president-elect of the International League.

In 1938 he founded the periodical *Archivos Argentinos de Reumatologia*, which is now in its 24th year, and as well as editing this journal, and publishing numerous books on the historical aspects of medicine and rheumatology, he contributed very many articles to medical journals throughout the world, as reference to the *Annals* Abstracts Section will quickly show.

His many friends amongst his fellow rheumatologists missed his presence and that of his gracious wife, Luisa Allende de Ruiz Moreno, at the Tenth International Congress in Rome in September, when he was to have been elected president for the ensuing four years.

DR. FRANÇOIS FRANÇON writes: Avec le professeur Anibal Ruiz Moreno disparaît une grande figure de la rhumatologie mondiale: il a été véritablement un des grands fondateurs de notre discipline en la République Argentine.

Il a été frappé le 22 décembre 1960, sur son "champ de bataille", comme le disait Corvisart en parlant de la mort de Bichat, alors qu'il présidait un séminaire dans sa chaire d'Histoire de la Médecine.

Ruiz Moreno était né à Cordoba (Argentine) le 31 mai 1907, et il avait fait ses études médicales à la Faculté de Buenos-Ayres où il avait soutenu, en 1932, une thèse remarquée sur "les relations entre les secrétions internes et externes du pancréas". Il s'était ensuite consacré à l'Histoire de la Médecine et à la Rhumatologie.

A ce dernier titre il avait créé la Ligue Argentine contre le Rhumatisme, qui est devenue maintenant la Société Argentine de Rhumatologie: elle m'a accordé la faveur d'être élu membre d'honneur. Il avait été fondateur, puis Vice-Président et enfin Président de la Ligue Panaméricaine contre le Rhumatisme: il avait été élu Président-désigné de la Ligue Internationale contre le Rhumatisme pour la période 1961-1965, et, en cette qualité, il devait assurer la Présidence du Congrès de Rome les 3-7 septembre 1961; un sort cruel lui a enlevé ce couronnement mérité de ses efforts et de toute une vie de labeur.

Il a fondé le Centre Antirhumatismal de Buenos-Ayres et les *Archivos Argentinos de Reumatologia*, organe trimestriel, qui atteint sa 24° année d'existence. Il a écrit quatre livres et plus de cent-cinquante articles sur la rhumatologie; il a dirigé de nombreux cours et il a été Rapporteur à maints congrès nationaux et internationaux: il était membre d'honneur de dix-sept Sociétés étrangères de Rhumatologie.

Son activité n'a pas été moindre dans le champ national et international d'Histoire de la Médecine dont il était professeur titulaire depuis 1947.

Nous avions eu la bonne fortune de le rencontrer à différents congrès; en même temps qu'un grand savant, il était un hidalgo accompli et il incarnait merveilleusement le type physique, les qualités et les aspirations de la belle race argentine.

Que sa veuve et sa famille veuillent bien trouver ici l'expression de nos condoléances émues et de notre vive gratitude.

Ann. rheum. Dis. (1961), **20**, 299.

ABSTRACTS

This section of the ANNALS *is published in collaboration with the two abstracting Journals,* ABSTRACTS OF WORLD MEDICINE, *and* OPHTHALMIC LITERATURE, *published by the British Medical Association.*

The abstracts selected for this Journal are divided into the following sections: Acute Rheumatism; Chronic Articular Rheumatism (Rheumatoid Arthritis, Osteo-Arthritis, Spondylitis, Miscellaneous); Disk Syndrome; Gout; Pararheumatic (Collagen) Diseases; Non-articular Rheumatism; General Pathology; ACTH, Cortisone, and other Steroids; Other General Subjects. At the end of each section is a list of titles of articles noted but not abstracted. Not all sections may be represented in any one issue.

The section "ACTH, Cortisone, and other Steroids" includes abstracts and titles of articles dealing with research into the scope and modus operandi *of steroid therapy.*

Acute Rheumatism

Clinical Aspects of Rheumatic Fever in Children. [In Russian.] SOLOMATINA, O. G., KLAJŠEVIČ, G. I., LEVINA, S. M., and IVANOVA, A. A. (1960). *Sovetsk. Med.*, **25**, 3. 2 figs, 13 refs.

In the authors' experience the clinical picture of rheumatic fever in children has definitely changed in recent years. They base this view on 1,472 cases of the disease in children treated during the period 1953 to 1959, among whom they noted a tendency to an increased incidence among children of pre-school age. Involvement of the joints was much less common in 1959 (12 per cent.) than in 1953 (52 per cent.) and when it did occur it was mild and of short duration. On the other hand involvement of the vascular system was more frequent, especially in cases with atypical joint lesions, such as arthritis of a single joint or involvement of small joints only. The incidence of endomyocarditis also increased (from 45·4 per cent. of 140 cases in 1953 to 73·13 per cent. of 186 cases in 1959), while that of pancarditis diminished (from 6·4 per cent. of 140 cases in 1953 to only 1·07 per cent. of 186 cases in 1959). Clinically the endomyocarditis developed early (between the 5th and 7th day) and gave rise to murmurs, but not always to permanent valvular damage. At some time during the disease the electrocardiogram showed increased atrioventricular conduction time in 57·0 per cent. of cases and of prolonged intraventricular conduction time in 77·4 per cent. Persistent increase of the QRS interval was observed in 27 per cent. of patients, prolongation of systole in the acute stage in 90 per cent. (although this persisted in only 7 per cent.), a low-voltage P-wave in 82 per cent., and a low-voltage T-wave in 93 per cent. (the latter recovered slowly in 66 per cent.), while other irregularities of rhythm were seen in a few cases only.

In 1959, also, lesions other than cardiac were observed fairly frequently, but their prognostic significance was less serious; lesions of the lung and pleura were rare. Leucocytosis and neutrophilia were more marked in the presence of polyarthritis, polyserositis, and abdominal lesions. In young children the erythrocyte sedimentation rate sometimes remained normal; in 75·5 per cent. of these patients the onset was acute, but the course was benign and lasted less than 2 months. Over-all the proportion of acute cases fell from 88·4 per cent. in 1953 to 55·3 per cent. in 1959, and no fulminant cases were seen in the latter year. Among the other changes seen in 1959 were an increased incidence of mild chorea or chorea associated with cardiovascular involvement, and a lower incidence of septic complications. Of the 1,472 young patients treated, eighteen aged between 7 and 15 years died. Of these, two were admitted to hospital late in the first attack with cardiac failure of Grade II or III, but the other deaths occurred in the third to seventh attacks. The immediate cause of death in all cases was pancarditis and circulatory failure. The authors express the view that diagnostic difficulties seem to have increased with the increased incidence of the disease and to this factor they attribute the recently noted tendency to diagnose rheumatic fever on insufficient grounds. *S. W. Waydenfeld.*

Rheumatic Fever in Children under 5 Years of Age. (La maladie de Bouillaud chez l'enfant de moins de 5 ans.) NEIMANN, N., PIERSON, M., LASCOMBES, G., PETIT, J., and VIVIER, F. (1960). *Arch. franç. Pédiat.*, **17**, 1024. 19 refs.

This is the report of a study of twenty cases of acute rheumatism in children, eight boys and twelve girls, under the age of 5 years observed during 8 years at the Clinique Médicale Infantile, Nancy. During the same period 297 children aged from 5 to 15 years were treated for acute rheumatism at the clinic. Of the twenty children, three were aged 2, seven aged 3, and ten aged 4. In eight cases the onset of the disease was with a typical polyarthritis, but in twelve there were no joint symptoms, the commonest symptoms in this group being dyspnoea, cyanosis, precordial pain, and cough; fever was not striking. Only three of the eight with arthritis had clinical evidence of carditis, in the form of an apical systolic murmur, but all the twelve without arthritis showed abnormal cardiac physical signs, all having an apical systolic murmur and one an aortic diastolic

murmur, while a gallop was heard in seven and pericardial friction in two. Nodules and erythema marginatum were not seen. All twelve children with no arthritis at onset developed permanent cardiac lesions, whereas five of the eight who presented with arthritis recovered with a clinically normal heart.

C. Bruce Perry.

Uro-precipitation Reaction in Rheumatic Fever in Children. (La reaction d'uro-precipitation dans la maladie de Bouillaud chez les enfants.) HIRSZFELD, H., BLOCH, B., KOZIOROWSKI, C., SASS, J., and WASIK, R. (1960). *Arch. franç. Pédiat.*, **17**, 1034. 4 figs, 13 refs.

The "uro-precipitation reaction", which was first observed by two Polish authors independently in 1942 in patients with typhus fever and later reported by Hirszfeld and Slomaska in 1950, consists in the precipitation of a substance in the patient's urine by the patient's own serum. It has now been shown to be strongly positive in patients with acute rheumatism, and the present report described further studies carried out at the Paediatric Clinic, Warsaw. The urinary factor has been labelled "urogene" and the serum factor "reagin". The reaction is absent in patients treated with salicylates and steroids and is abolished if either of these substances is added to the urine or serum, and it does not occur in patients with chorea or in the presence of cardiac failure. It was found to be positive in some patients with other diseases, such as pneumonia and infective hepatitis, but at a lower titre than in acute rheumatism. In the latter disease the authors state that the reaction was positive in 89·2 per cent. of cases and negative in 16·8 per cent. [*sic*]. It is suggested that in doubtful cases of acute rheumatism a positive reaction is of diagnostic significance. A similar reaction was obtained by using a dilute solution of streptolysin or hyaluronidase instead of the patient's urine. Attempts to isolate the "urogene" yielded a substance that appeared to be a polysaccharide, which was separable into five fractions by electrophoresis. The methods are described.

C. Bruce Perry.

Lesions of Apparently Healthy Skin during Rheumatic Fever in Children. (Lésions de la peau apparemment saine au cours de la maladie rhumatismale chez les enfants.) LEWENFISZ-WOJNAROWSKA, T., JABLONSKA, S., and ZAORSKA, B. (1960). *Arch. franç. Pédiat.*, **17**, 655. 6 figs, 4 refs.

The authors report from the Paediatric and Dermatological Clinics, Warsaw, that histological examination of the apparently healthy skin of children suffering from rheumatic fever revealed that there was oedema of the connective tissue, with lymphocytic and histiocytic infiltration of varying degree, and also some oedema of the vessel walls. These changes were already present during the first attack and became more marked after subsequent attacks; during clinical remission, however, they diminished in severity. In two children with chronic progressive rheumatoid arthritis no oedema or cellular infiltration was seen in the skin, but vascular changes and degeneration of elastic fibres were observed. The histological changes occurring during an attack of rheumatic fever improved or disappeared on treatment with corticosteroids, which also initiated clinical improvement. It is suggested that these steroids act on the mesenchymal tissue of the skin and it is thought probable that a similar action occurs in other mesenchymal tissues, such as that of the vascular system, which is affected in rheumatic fever. *G. W. Csonka.*

Relationship of Aschoff Bodies in Cardiac Atrial Appendages to the Natural History of Rheumatic Heart Disease. DALLDORF, F. G., and MURPHY, G. E. (1960). *Amer. J. Path.*, **37**, 507. 7 figs, 35 refs.

The authors have investigated the relationship between the preoperative clinical course and the occurrence of Aschoff bodies in the left auricular appendage removed at commissurotomy in patients with rheumatic heart disease.

The study covered records of 81 patients (64 women and 17 men aged 20 to 40) collected from the files of the New York Hospital. Histologically, the cases were divided into two groups according to whether Aschoff bodies were or were not present. [In the description of Aschoff bodies as seen in this material the authors categorically state that these bodies originate from "rheumatic injury to heart muscle", either striated or smooth, mostly in or just beneath the subendocardium. Such an origin is by no means generally agreed; for a recent critical discussion see Ehrlich (*Ann. N.Y. Acad. Sci.*, 1960, **86**, 1006).] Clinical division was into three groups:

Group 1 showed steady progression of cardiac symptoms for 18 months or less before operation;
Group 2 showed similar deterioration but for a longer period;
Group 3 had severe rheumatic heart disease, but without deterioration for the last 2 years.

Groups 1 and 2 were each subdivided into (A) those with definite progression of symptoms, and (B) those with only minimal and indefinite progression.

Of the total of 81 cases, fifty are reported to have had Aschoff bodies. In clinical Group 3, five out of thirteen patients showed such bodies, while in Subgroup 1A positive results were obtained in nineteen out of twenty, and in Subgroup 2A in thirteen of seventeen patients. Thus a relationship appears to have been established between the clinical course and the incidence of Aschoff bodies in rheumatic heart disease. *G. Loewi.*

Evolution of Heart Disease in Children: 5-year Report of a Co-operative Clinical Trial of ACTH, Cortisone, and Aspirin. MEDICAL RESEARCH COUNCIL OF GREAT BRITAIN AND AMERICAN HEART ASSOCIATION (1960). *Brit. med. J.*, **2**, 1033. 11 refs.

A study has been made at the end of 5 years after the conclusion of treatment of the 497 children who were admitted to the U.K./U.S. co-operative clinical trial of the relative merits of ACTH, cortisone, and aspirin in the treatment of acute rheumatic fever [see *Abstr. Wld Med.*, 1955, **18**, 225]. 445 of the cases (89·5 per cent.) were followed for the complete 5 years, and the status

of the heart was known for 426 of them. Only sixteen (3·2 per cent.) had died, fourteen of them from rheumatic heart disease; 36 (7·2 per cent.) were untraced. The very low fatality rate is striking. At the end of 5 years there is no evidence, on the treatment schedule used in this study, that the prognosis has been influenced more by one treatment than another. This confirms the findings reported at one year.

The major factor in determining the incidence of rheumatic heart disease at the end of 5 years is the status of the heart at the time treatment was begun. For cases without carditis initially the prognosis was excellent, since in 96 per cent. there was no residual heart disease. In cases with carditis initially, but without pre-existing heart disease, the proportion without residual heart disease decreased progressively from 82 per cent. for those with only a grade-1 apical systolic murmur to 30 per cent. for those with failure and/or pericarditis. In cases with pre-existing heart disease the prognosis was poor. Only 30 per cent. of those without pericarditis or failure and none of those with pericarditis and/or failure were without heart disease at 5 years. Cases with carditis and without pre-existing heart disease which had recurrences demanding re-treatment during the follow-up period had on the average a more severe cardiac status at start of treatment than did those without recurrences requiring re-treatment. At 5 years a larger proportion of these re-treated cases had murmurs.

These results make it clear that treatment of acute rheumatic fever cannot be properly evaluated unless the status of the heart of the patients at the start of treatment is taken closely into account.—[*Authors' summary.*]

Sydenham's Chorea: Its Relationship to Rheumatic Infection and Psychological Illness. MATTHEWS, R., WILLIAMS, H., RICKARDS, W., WATERHOUSE, I., and ALLAN, J. (1960). *Med. J. Aust.*, **2**, 771. 19 refs.

Twenty consecutive cases of chorea admitted to the Royal Children's Hospital, Melbourne, were investigated by a paediatrician, a psychiatrist, a psychologist, and a social worker in an attempt to determine possible psychological and social aetiological factors. The patients' ages ranged from 4 to 13 years; seven were boys and thirteen girls. Of the twenty patients, eight had had one or more previous attacks of chorea; three gave a history of past rheumatic infection, one of whom had a cardiac murmur; five had carditis during the attack of chorea, and one of these had erythema marginatum. In the subsequent 3 years two patients had further attacks of carditis and one developed a heart lesion. In sixteen cases there was a raised antistreptolysin-O titre and in ten a raised erythrocyte sedimentation rate. The electroencephalogram (EEG) was abnormal in sixteen, but there was no correlation between the severity of the chorea (or the side affected in the six patients with hemichorea) and the changes in the EEG. Of thirteen cases so examined, 5 to 18 months after cessation of the chorea, the EEG was normal in three, less abnormal in four, unchanged in five, and worse in one. Psychiatric and psychological data were obtained in nineteen of the twenty cases. The average intelligence quotient of the group was significantly below that of the general population, and the group as a whole showed difficulties in educational achievement and school adjustment. Of the nineteen patients, seventeen showed a common personality pattern, being self-conscious, insecure, overdependent on adults, and afraid of their own aggressive feelings. Family maladjustment was consistently present. The fathers' occupations varied from unskilled to semi-professional work. Thirteen of the families had suffered financial difficulties in the previous 5 years, and half were in current financial distress. *C. Bruce Perry.*

Blood Penicillin Levels after the Injection of Benzathine Penicillin in the Prophylaxis of Rheumatic Fever: a Critical Study. (Pénicillinémies après benzathine pénicilline injectable dans la prophylaxie du rhumatisme articulaire aigu. Étude critique.) CARRON, R., MAILLARD, M. A., and PELLERAT, J. (1961). *Pédiatrie*, **46**, 153. 14 refs.

Epistaxis: Comparative Study of its Incidence in Rheumatic Fever and in a Control Group. (Epistaxes: estudo comparativo da incidencia em febre reumática a grupo controle.) DE MEDEIROS NETO, G. A., and DE OLIVEIRA PENNA, D. (1960). *Rev. paul. Med.*, **57**, 373. 5 figs, 13 refs.

Study of Rheumatic Fever in Infancy. (Studio sulla malattia reumatica nell'infanzia.) CAVALIERI, S. (1961). *Fracastoro*, **54**, 1. 119 refs.

Prevention of Recurrences of Rheumatic Fever in the Army. (Prévention des rechutes du rhumatisme articulaire aigu dans l'armée.) CROSNIER (no initial) (1961). *Rev. Cps Santé milit.*, **2**, 3.

Chronic Articular Rheumatism (Rheumatoid Arthritis)

Intra-articular Nitrogen Mustard Treatment of Rheumatoid Arthritis. [In English.] VAINIO, K., and JULKUNEN, H. (1960). *Acta rheum. scand.*, **6**, 25. 1 fig., 10 refs.

The object of the investigation here described was to determine whether, in rheumatoid arthritis, intra-articular injections of nitrogen mustard combined with hydrocortisone gave better results than injections of hydrocortisone alone. The study was carried out, at the Rheumatism Foundation Hospital, Heinola, Finland, on 59 patients with two joints symmetrically involved; where one joint appeared to be more severely involved, it was used for the nitrogen mustard injection.

The contents of one ampoule of nitrogen mustard (10 mg.) were diluted to 10 ml. with normal saline; for injection into a knee-joint, for example, 0·5 ml. (0·5 mg.) of the solution was mixed with 25 mg. hydrocortisone. Injections were given weekly in series of three or six, but in the latter case an interval of 3 weeks was allowed after the first three injections. An equal amount of

hydrocortisone was injected into the corresponding joint. A number of objective and subjective tests were devised and joints graded both before and after injection. In 32 per cent. the combination gave better results than hydrocortisone alone. The best results were obtained in patients with minimal radiological changes—that is, those in whom hydrocortisone alone produced but little effect. *D. Preiskel.*

Pregnancy and Rheumatoid Arthritis. [In English.] SMITH, W. D., and WEST, H. F. (1960). *Acta rheum. scand.*, **6**, 189. 2 figs, 15 refs.

In a forward-going study of the effect of pregnancy on eleven patients with rheumatoid arthritis and one with ankylosing spondylitis assays have been made for urinary excretion of total 17-hydroxycorticosteroids (17(OH)CS), 17 ketosteroids, and 21-deoxy-17-20 ketols.

It has been found that the definite remissions in disease activity occurred during the third trimester when the excretion of total 17(OH)SC rose markedly in most patients. It has been deduced from the magnitude of the increase that there must have been a considerable increase in the adrenal secretion of cortisol. Since four patients enjoyed a remission of symptoms without evidence of an appreciable increase in cortisol secretion it is thought that an increased secretion of cortisol alone cannot account for all the pregnancy remissions. It is pointed out that there is evidence as yet unconfirmed, of a rise in the diffusible fraction of circulating plasma cortisol during pregnancy. If this is confirmed, by further studies of the diffusible fraction in the blood or by studies of the amount of cortisol filtered off in the renal glomeruli, it is likely that this, and the increased secretion of cortisol, will prove to be the pregnancy factors that relieve rheumatoid arthritis.—[*Authors' summary.*]

Diagnosis of Rheumatoid Arthritis. RUFF, J. DOUGLAS (1961). *J. Kentucky med. Ass.*, **59**, 237. 4 figs, 3 refs.

Synthetic Antimalarials in the Treatment of Rheumatoid Arthritis. (Étude sur l'emploi et le mode d'action des antimalariques de synthèse dans le traitement de la polyarthrite chronique évolutive.) LACAPÈRE, J., MONIER, H., BONHOMME, F., and DELAVILLE, G. (1961). *Rev. Rhum.*, **28**, 1. 22 refs.

Action of Synthetic Antimalarials combined with Physiotherapy in Rheumatoid Arthritis. (Étude de l'action des antipaludéens de synthèse associés à la physiothérapie dans la polyarthrite chronique évolutive.) BALMUS, P., CORASIEVICI, V., and POPOVICI, N. (1961). *Rev. Rhum.*, **28**, 38. 6 refs.

Phenylbutazone in Antirheumatic Therapy. (Butazolidina en la terapéutica antirreumática.) MARENGO, R. (1961). *Rev. argent. Reum.*, **25**, 346. 15 refs.

Place of Chloroquine in the Treatment of Arthritis of Rheumatic Origin. (La position de la chloroquine dans la thérapie de l'arthrite rhumatismale.) GALLI, T. (1960). *J. belge Méd. phys. Rhum.*, **15**, 237.

Need for Early Treatment of the Rheumatoid Hand. SWANSON, A. B. (1961). *J. Mich. med. Soc.*, **60**, 348. 4 figs, 5 refs.

Surgical Treatment of the Rheumatoid Hand. HENDERSON, E. D., and LIPSCOMB, P. R. (1961). *J. Amer. med. Ass.*, **175**, 431. 5 figs, 18 refs.

Clinical and Statistical Observations on the Psammatotherapy of Rheumatic Joint Diseases. (Rilievi clinico-statistici sul trattamento psammatoterapico delle artropatie reumatiche.) LEDRI, G., and SOLDATI, R. (1961). *Minerva med.* (*Torino*), **52**, 973. 7 refs.

Renal Papillary Necrosis in Rheumatoid Arthritis. (Papillitis necroticans renalis ved reumatoid artrit.) CLAUSEN, E., and PEDERSEN, J. (1961). *Ugeskr. Læg.*, **123**, 622. 16 refs.

Leg Ulcers in Rheumatoid Arthritis. Use of Pressure-Gradient Therapy, High-Protein Diet, and Other Measures produces Successful Results. BENINSON, J., and ENSIGN, D. C. (1961). *J. Amer. med. Ass.*, **175**, 437. 3 figs, 9 refs.

Chronic Atypical Polyarthritis and its Treatment. (Les polyarthrites chroniques atypiques et leur traitement.) BICKEL, G. (1961). *Rev. méd. Suisse rom.*, **81**, 253. 70 refs.

(Osteo-Arthritis)

Treatment of Osteo-Arthritis of the Hip by Mobilization under General Anaesthesia followed by Functional Re-education. (Traitement de la coxarthrose par mobilisation sous anesthésie générale suivie de rééducation fonctionnelle.) DE SÈZE, S., and DENIS A. (1960). *Rev. Rhum.*, **27**, 182. 1 fig.

The treatment of fifteen patients with osteo-arthritis of the hip by the method of Staudinger, which consists in manipulation under general anaesthesia followed by graduated intensive, physical treatment, is described. In carrying out the procedure, the hip-joint of the anaesthetized patient is slowly flexed in adduction to the maximum extent, this movement being followed by rotation and then by abduction of the extended leg. After the manipulation the legs are immobilized in abduction for 36 hours, during which time analgesics are necessary. Thereafter the patient is shown how to perform static contractions of the muscles of the trunk and thighs; on the third day he sits over the edge of the bed, and on the fourth he may walk a few paces with the help of an appliance. At this stage, correction of the gait is important; walking distance may then be gradually increased. After about 2 weeks the patient is ready for

transfer to a rehabilitation centre for further intensive treatment. Non-manual occupations can usually be resumed during the third month after manipulation. Of the fifteen patients so treated, five achieved appreciable increase in range of movement and disappearance of pain, six showed partial amelioration, but four were not benefited. It is noted that the presence of osteoporosis or a past history of phlebitis or other vascular disorder is a contra-indication to this form of treatment.

In the authors' opinion this treatment is of most benefit, on the one hand to the patient aged about 50 with unilateral and early osteo-arthritis of the hip, and on the other to the older patient with bilateral disabling arthritis of the hips, who is too old for surgical treatment but is otherwise healthy; in such cases the deformity can be corrected and pain is often much relieved. Further work is needed, however, to assess more accurately the value of the method. *B. E. W. Mace.*

Morbid Anatomy of Cervical Spondylosis and Myelopathy. WILKINSON, M. (1960). *Brain*, **83**, 589. 26 figs, bibl.

In a long paper the author, after reviewing the literature, discusses the frequency of cervical spondylosis and its associated symptoms. She then describes an anatomical and pathological study of seventeen patients who came to necropsy at the London Hospital, the entire cervical spine and upper dorsal vertebrae being removed intact in a single block, fixed for 4 weeks, and dissected in stages. The changes found in the spinal canal, vertebrae, and intervertebral disks are described, and the question of compression of nerve roots and spinal cord and the significance of trauma and disturbed vascular supply are considered at length. Six illustrative case histories are given.

The author concludes that cervical spondylosis is the most common cause of pain in the neck and arm and of a spastic paraplegia in the middle-aged and elderly. She suggests that the primary lesion is a degeneration of the intervertebral disks, and that the changes in the vertebral bodies and neurocentral joints are secondary to this. Changes also occur in the annulus fibrosus, the vertebrae, the region of the intervertebral foramina, and the nucleus pulposus, and these in turn may cause lesions in the nerve roots and cord. No evidence was found that thrombosis of the anterior spinal artery plays a part in producing the lesions. *R. Wyburn-Mason.*

Osteo-Arthritis and Old Age. STECHER, R. M. (1961). *Geriatrics*, **16**, 167. 19 refs.

Morphological Constitution in Osteo-Arthritis. (La costituzione morfologica nella malattia osteo-artrosica.) BASSO, F., BORGO, E., and CAPPONI, G. (1961). *Minerva med. (Torino)*, **52**, 1277. 50 refs.

Treatment of Osteo-Arthritis of the Knees. RHINELANDER, F. W. (1960). *Arthr. and Rheum.*, **3**, 561.

Treatment of Osteo-Arthritis of the Knees. HOLLANDER, J. L. (1960). *Arthr. and Rheum.*, **3**, 564.

Osteo-Arthritis and Symptomatic Arthritis. HERRELL, W. E. (1961). *J. Kentucky med. Ass.*, **59**, 241. 1 fig.

Association of Osteo-Arthritis and Diabetes Mellitus. WAINE, H., NEVINNY, D., ROSENTHAL, J., and JOFFE, I. B. (1961). *Tufts Fol. med.*, **7**, 13. 3 figs, 7 refs.

Surgery in Necrosis of the Femoral Head. (Traitement chirurgical de l'ostéonécrose de la tête fémorale.) DEBEYRE, J., SÈZE, S. DE, and SCHLOGEL, G. (1961). *Rev. Rhum.*, **28**, 17. 9 figs.

Male Sex Hormone and Osteo-Arthrosis in Mice. SILBERBERG, R., and SILBERBERG, M. (1961). *J. Bone Jt Surg.*, **43A**, 243. 6 figs, 12 refs.

(Spondylitis)

Cervical Vertebral Erosions and Subluxations in Rheumatoid Arthritis and Ankylosing Spondylitis. MARTEL, W., and PAGE, J. W. (1960). *Arthr. and Rheum.*, **3**, 546. 7 figs, 23 refs.

The authors of this paper from the University of Michigan, Ann Arbor, point out that, although it has been known for some time that in ankylosing spondylitis and in juvenile rheumatoid arthritis the cervical spine is not infrequently involved, the fact that this is also true in many cases of rheumatoid arthritis of adult type has received less serious attention. They assert that the potentially dangerous complication of atlanto-axial subluxation has received too little notice in its earlier stages, which can be detected in many cases of established or even early disease.

In no less than fifteen of 25 patients who complained of cervical pain in association with severe rheumatoid arthritis the authors were able to demonstrate the existence of some degree of cervical subluxation by means of lateral radiographs taken with the neck both in flexion and in full extension. The subluxation most commonly affected the atlanto-occipital joint, but vertebral erosions, particularly of the odontoid process, were also observed in all but one of these patients, while in seven cases there was also vertical displacement of the whole cervical spine in relation to the skull. The authors explain the infrequent occurrence of neurological evidence of the presence of such lesions by the slow development of the erosive lesions, the destruction of the odontoid process, which allows more room for the spinal cord, and the avoidance of full flexion by the patient.

W. S. C. Copeman.

Association between Ulcerative Colitis, Regional Enteritis, and Ankylosing Spondylitis. ACHESON, E. D. (1960). *Quart. J. Med.*, **29**, 489. 29 refs.

During an epidemiological study of ulcerative colitis and regional enteritis in United States veterans, a surprising number of patients were found to have ankylosing

spondylitis in addition. Data were obtained from all 2,320 patients discharged from Veterans Administration hospitals with regional enteritis between 1953 and 1957, and ulcerative colitis in 1956 and 1957. It was found that 31 of the cases of colitis (representing 2·6 per cent. of discharges) and 22 of the cases of enteritis (representing 3 per cent. of discharges) had spondylitis. This diagnosis of spondylitis was made twenty times as often as in a 25 per cent. systematic sample of all patients admitted to Veterans Administration hospitals. Information was also collected regarding two other chronic diseases; thus among 675 admissions for Hodgkin's disease no cases of spondylitis were found, and in 813 cases of disseminated sclerosis there were only two of spondylitis.

The author gives in detail the diagnostic criteria for the conditions under discussion. He notes that 24 patients with spondylitis showed the classic picture of the advanced stage of the disorder, with obliteration of the sacro-iliac joints and extensive ankylosis of the spine. In the majority of cases the spondylitis preceded the abdominal condition. Deep irradiation had been given in fourteen cases, but in eight this was after the onset of the enteritis or colitis; in only six cases out of the total could irradiation have played any part in the development of these conditions. *K. C. Robinson.*

Surgical Treatment of Tuberculous Spondylitis. [In Russian.] JUDIN, JA. B. (1960). *Probl. Tuberk.*, **38**, 59.

The author describes the methods employed in the surgical treatment of 75 patients (46 adults and 29 children) with tuberculous spondylitis operated on since May, 1956. The indication for surgical treatment (in addition to other forms of therapy) was primary osteitis of the bodies of the vertebrae, or the presence of abscesses, paralysis, and chronic sinuses. One contraindication is the young age of the patient, transversectomy being not recommended in children under the age of 10 years. In adults all abscesses are completely resected, especially if situated intrathoracically, and all caseous abscesses in children and adults are removed. Before operation treatment with PAS and phthivazid, and occasionally streptomycin, is given; this treatment is continued in the postoperative period for a considerable time, in many cases a total dose of as much as 70 to 80 g. streptomycin and 100 to 130 g. phthivazid being administered.

In regard to complications, seven patients developed a pneumothorax after the operation, while in several cases of lumbo-iliac abscess the sciatic nerve was injured, but was successfully sutured. In the author's experience the radical excision of fresh foci of infection which are not complicated by abscesses or sinuses abruptly checks spread of the disease and leads to a recession of the process, sometimes within 3 months, while evacuation of the multiple abscesses which complicate early tuberculous spondylitis reduces the course of treatment by 10 to 12 months. The draining of late abscesses definitely improves the condition of the patient. In conclusion the author describes in detail the various types of spondylitis encountered in these 75 patients. *H. W. Swann.*

Association of Five Cases of Ankylosing Spondylitis and Paget's Disease. (À propos de l'association cinq fois constatée de spondylarthrite ankylosante et de maladie de Paget.) LAYANI, J., FRANÇON, J., and WATTEBLED, R. (1961). *Sem. Hôp. Paris*, **37**, 1037. 12 figs, 2 refs.

(Miscellaneous)

Paranylene: Preliminary Experience with a New Anti-inflammatory Agent in Arthritis. POZNANSKI, W. J., and WALLACE, J. D. (1960). *Canad. med. Ass. J.*, **83**, 1302. 1 fig., 3 refs.

Paranylene (9(*p*-guanylbenzal) fluorene hydrochloride) has been shown in animal experiments to have anti-inflammatory effects and to be ten times more potent than phenylbutazone in inhibiting the formation of fibrous tissue. This report from the Wainwright Clinic, Wainwright, Alberta, gives the results of a short trial of paranylene on 22 patients with various types of chronic arthritis, including nine cases of rheumatoid arthritis and eight of osteo-arthritis, the rest including cases of spondylitis and gout. The drug was given by mouth in daily doses of 100 to 800 mg. for 4 to 36 weeks. Beneficial effects were observed in eighteen of the 22 cases, the only side-effect noted being gastro-intestinal irritation in two cases.

[Clearly a larger, controlled, trial will have to be carried out before the value of this drug can be assessed.] *Oswald Savage.*

Psoriatic Arthritis: a Roentgenologic Study. AVILA, R., PUGH, D. G., SLOCUMB, C. H., and WINKELMANN, R. K. (1960). *Radiology*, **75**, 691. 7 figs, 18 refs.

An investigation was carried out at the Mayo Clinic to determine whether psoriatic arthritis is a separate entity from rheumatoid arthritis. Radiographs of the hands, feet, and other joints of 155 patients with psoriasis and arthritic changes were compared with those of a control series of 100 patients with rheumatoid arthritis but without psoriasis. In the psoriatic group 31 per cent. showed lesions considered to be characteristic of the disease; in a further 31 per cent., such lesions were present in combination with others typical of rheumatoid arthritis, while in the remaining 38 per cent. the arthritic changes had a rheumatoid pattern. There was an increased incidence of rheumatoid arthritis in patients with psoriasis, this observation confirming the findings of other workers.

Radiological signs considered to be characteristic of psoriasis were:

(1) destructive arthritis affecting predominantly the distal interphalangeal joints of the fingers and the interphalangeal joints of the toes, these joints being relatively rarely affected in rheumatoid arthritis;
(2) bony ankylosis of these joints, a feature again rare at these sites in rheumatoid arthritis;
(3) marked widening of the affected joint spaces with sharp demarcation of the eroded bony margins, a finding which is virtually pathognomonic;

(4) bony proliferation round the base of the distal phalanx of the great toe with destructive arthritis of the interphalangeal joint, such changes being strongly diagnostic;

(5) resorption of distal phalangeal tufts.

Radiological changes such as these were very rarely seen in the control cases. The features of osteoporosis and ulnar deviation of the fingers were much less common than in the rheumatoid group. In very advanced cases of psoriatic arthritis severe joint destruction of the "cup and pencil" type could closely resemble the late stages of rheumatoid arthritis. Nevertheless, on assembling all the radiological evidence, the authors conclude that a characteristic form of arthritis often accompanies psoriasis. *R. O. Murray.*

Diagnosis and Therapy of Acute Suppurative Arthritis. WARD, J., COHEN, A. S., and BAUER, W. (1960). *Arthr. and Rheum.*, **3**, 522. 3 figs, 21 refs.

The case records of all patients with suppurative arthritis seen at the Massachusetts General Hospital from 1947 to 1957, totalling 24, have been reviewed. The patients' ages ranged from one to 75 years, but the frequency of the disease was highest in children and the aged. The sex incidence was approximately equal. In only five cases was the diagnosis of acute suppurative arthritis made on admission: rheumatoid arthritis was diagnosed in six cases, in three erroneously and in three correctly, though there was additional suppurative arthritis. In 21 cases the arthritis was monarticular, usually involving the knee. The local signs were tenderness, painful and limited movement, swelling, and heat. A demonstrable effusion was present in 22 cases and redness or erythema in fourteen. The source of infection was not always evident, but a haematogenous source was at least probable in 22 patients, including five with local non-penetrating trauma and the three with rheumatoid arthritis. One joint was infected by direct puncture and one by extension from osteomyelitis.

The joint fluid contained from 25,000 to 253,000 leucocytes per c.mm. with over 90 per cent. polymorphonuclear cells. In nine cases the difference between the sugar concentrations in the blood and synovial fluid ranged from 24 to 112 mg. per 100 ml. Culture of the synovial fluid was positive in eighteen instances, a staphylococcus being grown on eleven occasions. All the organisms were sensitive to antibacterial agents [but details of sensitivities are not given]. Twelve patients were treated with penicillin and the remainder with combinations of antibiotics or of antibiotics and sulphonamides. Local instillation of penicillin was performed in ten cases. Surgical drainage was carried out on four patients, only two of whom made a full recovery. Of the twenty others, seventeen made a complete recovery. Poor end-results were attributable to delay in treatment rather than to any other factor. The authors recommend the early systemic administration of antibiotics, repeated aspirations of large effusions, splinting, early passive movements, and later active exercises. *J. T. Scott.*

Relationship of Human Genital Pleuropneumonia-like Organisms to Arthritis complicating Urethritis. FORD, D. K. (1960). *Arthr. and Rheum.*, 3, 395. 25 refs.

The present study was undertaken at the University of British Columbia, Vancouver, in the hope that primary isolation of pleuropneumonia-like organisms (PPLO) from the joint fluid of patients with Reiter's disease might be achieved by means of human amnion tissue culture instead of directly with agar media. A total of fifteen synovial exudates from twelve patients with arthritis and urethritis failed to show PPLO by the tissue-culture method, nor was any cytopathogenic change seen in the amnion preparations. In addition, 240 patients, men and women, attending a venereal disease clinic with a variety of urogenital conditions were investigated by this method. From these cases 75 strains of PPLO were isolated, but no evidence was obtainable that PPLO were aetiologically related to non-gonococcal urethritis or Reiter's syndrome. *G. W. Csonka.*

Current Concepts in the Physical Management of Arthritis. ROTHMAN, L. M., and ROGOFF, J. B. (1961). *N.Y. St. J. Med.*, **61**, 396. 8 refs.

Clinical Manifestations of Infection with Group-A Arthropod-borne Viruses in Queensland. DOHERTY, R. L., ANDERSON, S. G., AARON, K., FARNWORTH, J. K., KNYVETT, A. F., and NIMMO, D. (1961). *Med. J. Aust.*, **1**, 276. 9 refs.

Epidemic Polyarthritis: Antibody to a Group-A Arthropod-borne Virus in Australia and the Island of New Guinea. ANDERSON, S. G., DOHERTY, R. L., and CARLEY, J. G. (1961). *Med. J. Aust.*, **1**, 273. 1 fig., 11 refs.

Chronic Rheumatoid Polyarthritis and Spondylarthritis associated with Neurological Symptoms and Signs occasionally simulating an Intraspinal Expansive Process. HAUGE, T. (1961). *Acta chir. scand.*, **120**, 395. 15 figs, 5 refs.

Radiology of Rheumatic Joint Diseases. (Radiología de las artropatías reumáticas.) MOREAU, J. (1961). *Rev. argent. Reum.*, **25**, 357.

Rheumatoid Cysts of the Calf and their Relation to Baker's Cysts of the Knee. MAUDSLEY, R. H., and ARDEN, G. P. (1961). *J. Bone Jt Surg.*, **43B**, 87. 2 figs, 7 refs.

Neuralgia due to Periarthritis. (Über periarthritisch bedingte Neuralgien.) GUKELBERGER, M. (1961). *Schweiz. med. Wschr.*, **91**, 451. 8 figs, 8 refs.

Traumatic Rupture of the Rotator Cuff: A Clear-cut Anatomical and Clinical Form of "Periarthritis of the Shoulder". (Les ruptures traumatiques de la coiffe des rotateurs: une forme anatomoclinique bien précise de la "périarthrite de l'épaule".) DE SÈZE, S., CAROIT, M., RYCKEWAERT, A., POINSARD, G., RENIER, J. C., HUBAULT, A., and WELLING, I. (1960). *J. belge Méd. phys. Rhum.*, **15**, 223. 16 figs.

Periarthritis produced in Rats with Freund's Adjuvants. SILVERSTEIN, E., and SOKOLOFF, L. (1960). *Arthr. and Rheum.*, **3**, 485. 6 figs, 17 refs.

Disk Syndrome

Visceral Manifestations of Vertebral Disk Degeneration. (Le retentissement viscéral de la discopathie vertébrale dégénérative (vérification expérimentale).) BERCOVICI, S., and FONI, I. (1961). *Rev. Rhum.*, **28**, 34. 4 figs, 4 refs.

Gout

Effect of Intravenous Administration of Crystalline Pancreatic Desoxyribonuclease in Patients with Gout. AYVAZIAN, J. H., and AYVAZIAN, L. F. (1960). *New Engl. J. Med.*, **263**, 999. 5 refs.

The authors of this paper fron New York University School of Medicine describe a study of the effect of intravenous administration of crystalline pancreatic deoxyribonuclease in sixteen patients with hyperuricaemia and a history of gout, fifteen convalescent patients without evidence of hyperuricaemia serving as controls. The patients in both groups received an intravenous injection of 22 mg. of pancreatic deoxyribonuclease immediately after a control blood sample had been withdrawn and again 12 hours later. This dose has an activity of approximately 2,000,000 viscosimetric units and maintains significant enzymic activity in the blood for 12 hours. A 24-hour specimen of urine was collected before and after administration of the enzyme. Both patients and controls were given a low-purine diet. During the test and for at least a week before it none of the patients received any drugs likely to effect uric acid metabolism. The serum uric acid level was estimated at 4, 8, 12, and 24 hours after the first injection.

It was found that 24 hours after the injection of the enzyme the changes in the serum uric acid level in the normal (non-hyperuricaemic) patients varied between −0·3 mg. and +0·9 mg. per 100 ml., the mean change being +0·22 mg. The increase, although small, occurred in twelve of the fifteen controls, only two showing a decrease. These variations were significant on statistical analysis, but no such changes were observed in the urinary excretion of uric acid. In the gouty patients an opposite trend was observed. At 24 hours after the injection the changes in the serum uric acid level ranged from −1·5 mg. to +0·1 mg. per 100 ml., the mean change being −0·76 mg. per 100 ml. Only one of the sixteen patients showed a rise in the serum uric acid level. In eight of the patients the 24-hour excretion of uric acid changed in amounts varying from −8 mg. to +490 mg., with a mean increase of 164 mg. In two patients excretion decreased and in one it was unchanged; satisfactory 24-hour specimens were not obtained from the remaining five patients. It was noted that in gouty patients who were asymptomatic there was only slight to moderate variation in the serum uric acid level while the urinary excretion of uric acid showed no significant change. In contrast, a much greater degree of change in the serum level and in the 24-hour urinary excretion of uric acid was observed in the nine patients who had symptoms of gout at the time of the trial.

The authors consider that the decrease in the serum uric acid level accompanied by a rise in the urinary excretion resulting from intravenous administration of pancreatic deoxyribonuclease indicates a uricosuric action of the enzyme in gouty patients and that this uricosuric effect appears to be related to the degree of inflammation present. Unlike other uricosuric agents this enzyme has no effect in non-gouty subjects. Previous workers have shown that pancreatic deoxyribonuclease mobilizes nucleic acids from areas of inflammation—for example, in pulmonary abscesses—and that it is capable of diffusing readily into areas where suppuration or inflammation is present.

It is stated that the mechanism whereby uric acid production increases but the serum concentration decreases is obscure and is being further studied.

J. Warwick Buckler.

Treatment of Gout with Zoxazolamine. (Traitement de la goutte par la zoxazolamine.) DE SÈZE, S., RYCKEWAERT, A., and KAHN, M. F. (1960). *Presse méd.*, **68**, 2329. 1 fig., 12 refs.

Zoxazolamine is a uricosuric agent with a rather short-lived action. It is almost completely metabolized in the body and little is excreted unchanged. The authors describe its effects in 25 patients, 24 of them men, with proven gout, fourteen of whom had tophi. The dosage was usually 125 mg. daily, rising to 250 mg. and then 375 mg. daily. As with other uricosuric agents zoxazolamine is known to increase the frequency of acute gouty episodes, especially at the start of treatment, and in an effort to prevent this 1 mg. colchicine was given daily in all cases together with the zoxazolamine.

It was found that zoxazolamine reduced the blood uric acid level to a significant degree in all the patients, most markedly in those with a high level before treatment. In the period before treatment the mean number of acute attacks was 0·4 per patient per month, whereas during treatment with zoxazolamine this figure was actually slightly reduced (0·35 per patient per month). The authors consider that, but for the suppressive effect of the colchicine given in association, the number of acute attacks would have been greatly increased. Zoxazolamine was well tolerated in the doses given and only minor side-effects, such as anorexia and headache, were noted. It was, nevertheless, necessary to stop treatment in three patients, two of whom developed renal colic. The authors conclude that zoxazolamine is an effective uricosuric agent, but suggest that further studies are necessary to determine its value in comparison with other similar drugs.

B. E. W. Mace.

Gout in Cyanotic Congenital Heart Disease. SOMERVILLE, J. (1961). *Brit. Heart J.*, **23**, 31. 2 figs, 16 refs.

Over a period of 5 years, nine cases of gout complicating cyanotic congenital heart disease were seen at the National Heart and Guy's Hospitals, London. The

sex incidence (eight males and one female) was similar to that in hereditary gout, in which 96 per cent. of the affected patients are men. All the patients were adults, the youngest being 18 and the oldest 69 years. Fallot's tetralogy, which was present in four of the patients, was the commonest cardiac lesion. The nine cases were found in a series of about 400 cases of cyanotic congenital heart disease, an incidence of approximately 2 per cent., which is five times the probable incidence (0·2 per cent. to 0·5 per cent.) in the general population. In all the patients at the time of the first attack the haemoglobin level was over 130 per cent. and the serum uric acid concentration was more than 6 mg. per 100 ml. It is considered that the development of gout is probably related to the degree of polycythaemia and to the age of the patient. In three of the four patients who had manifestations of gout before the age of 25 there was evidence of primary renal disease, which may be a further factor influencing the development of hyperuricaemia.

A. J. Karlish.

Critical Study of Gouty Rheumatism. (Étude critique du rhumatisme goutteux.) LAYANI, F., DURUPT, L., and CHAOUAT, Y. (1961). *Sem. Hôp. Paris*, **37**, 1055.

Trimethylcolchicinic Acid in the Treatment of Acute Gout. WALLACE, S. L. (1961). *Ann. intern. Med.*, **54**, 274. 1 fig., 24 refs.

Leg Ache: A Symptomatic Indication of Irregular Gout. PEPPER, H., and MANN, L. (1961). *Ann. intern. Med.*, **54**, 267. 6 refs.

Pararheumatic (Collagen) Diseases

Systemic Lupus Erythematosus. Description of 37 Cases in Children and a Discussion of Endocrine Therapy in 32 of the Cases. COOK, C. D., WEDGWOOD, R. J. P., CRAIG, J. M., HARTMANN, J. R., and JANEWAY, C. A. (1960). *Pediatrics*, **26**, 570. 10 figs, 11 refs.

The authors have reviewed 37 cases of systemic lupus erythematosus in patients aged under 14 seen between 1916 and 1959 at the Boston Children's Hospital and the Babies' and Children's Hospital, Cleveland. Of these children 34 were girls. In thirty cases the illness started between the ages of 9 and 13, and 27 of the children died within 8 weeks to 5½ years of the onset. In seven cases severe sore throat and in four considerable psychological stress preceded the illness.

A facial rash was present at some stage of the disease in 31 cases; nineteen patients presented with an erythematous rash, which was accompanied by fever and arthralgia in fifteen cases. In twelve cases there was intermittent arthralgia, sometimes with fever, for up to 3 years before the facial rash. In four children thrombocytopenia, in five renal manifestations, and in two cardiac failure were early features. Fulminating illness with death in 2 to 6 months occurred in five cases. The facial rash did not show the involvement of the upper eyelid and the oedema that are seen in dermatomyositis. In the later stages vesicular, bullous necrotic or haemorrhagic lesions sometimes developed; rashes resembling measles, drug eruption, and herpes zoster also occurred. Half the children developed erythematous macules on the hands and feet which were sometimes intensely pruritic. Some children had finger nail-bed changes. A quarter of the patients had partial alopecia. Oral and genital lesions were also observed. All but four patients showed renal involvement characterized by oedema and hypertension, which was an important factor in the death of eighteen. Hepatomegaly was noted in fifteen cases and significant splenomegaly in sixteen. Generalized lymphadenopathy was not prominent. Pericarditis occurred in three cases without uraemia. Pleural effusions and pneumonia were common, and cardiac abnormalities were noted in twenty cases. One-third of the patients had neurological symptoms, including convulsions, hemiplegia, and muscle weakness. In one case cytoid bodies were found in the fundus oculi.

Before antibiotics were available infections were troublesome and caused three deaths. In six cases there was difficulty in cross-matching blood, and some of these patients gave a severe reaction to transfusion of most carefully cross-matched blood.

The L.E. test gave positive findings in 31 of the 32 patients tested. Normochromic normocytic anaemia was common, and 20 per cent. of the children developed an anaemia with a haemoglobin level below 6 g. per 100 ml. Leucopenia with a cell count below 5,000 per c.mm. occurred in 21 cases, and the leucocyte response to infection was often decreased. Six patients had a biologically false serological reaction for syphilis. The latex-fixation test gave a negative response in the eight cases tested. Reticulocytosis up to 10 per cent. occurred following a favourable response to cortisone. Positive results were obtained in twenty of 22 children on whom liver flocculation tests were performed. The injection of leucocytes intradermally led to a delayed hypersensitivity reaction with redness and oedema within 48 hours.

All the fourteen cases examined *post mortem* showed involvement of the glomeruli or arterioles of the kidney. Libman-Sacks lesions occurred in seven cases. In ten cases plasma-cell hyperplasia was found in the spleen, bone marrow, or lymph nodes. Vascular involvement led to gastro-intestinal ulceration and infarctions of the liver, spleen, and pancreas. Haematoxylin bodies were seen in most cases.

Treatment included gold therapy, administration of bismuth and of nitrogen mustard, and irradiation. Of three children given nitrogen mustard, partial remission occurred in two. Cortisone was used in 32 cases. Because attempts to reduce the dose usually led to relapse, continuous treatment with high doses was employed. In six of the ten surviving patients cortisone treatment reversed abnormal urinary findings. Such reversal had not been observed by the authors in inadequately treated cases, but some renal lesions progressed in spite of steroid therapy.

The authors conclude that systemic lupus erythematosus is more severe in children than in adults. Because

of the poor prognosis of the disease and the evidence suggesting the value of steroid therapy, they advocate early and continuous treatment with high doses of steroid for several years even in the absence of symptoms.

G. L. Asherson.

Further Observation on Hepatitis and Cirrhosis in Young Women with Positive Clot Tests for Lupus Erythematosus. BARTHOLOMEW, L. G., CAIN, J. C., BAGGENSTOSS, A. H., and HAGEDORN, A. B. (1960). *Gastroenterology*, **39**, 730. 7 refs.

Three additional cases of an unusual disease of the liver occurring in young women with a positive lupus erythematosus clot test are reported. This disease is characterized by a distinct clinical syndrome which includes many of the following features: periodic fever, migratory polyarthritis, pleurisy, indeterminate abdominal pain, unusual sensitivity to sunlight and drugs, skin rashes, weakness, and fatigue. Later in the course of the disease, evidence of serious impairment of the liver, including jaundice, hepatosplenomegaly, and spider angiomas, overshadows some of the former systemic manifestations.

Typical laboratory findings in the fully developed syndrome include anaemia, frequently hemolytic in type; leucopenia; marked elevation of the sedimentation rate; marked hypergammaglobulinaemia; varying degrees of jaundice; significant abnormalities in the so-called liver function tests, including the cephalin flocculation and thymol and zinc turbidity tests; fixed elevation of the prothrombin time; false positive serologic reaction for syphilis; and abnormal urinary sediment. The clot test for lupus erythematosus has given repeatedly positive results.

Despite these clinical and laboratory abnormalities and the ultimate poor prognosis, patients present for a considerable time the appearance of good health, belying the seriousness of their illness. Death is due to hepatic insufficiency.—[*Authors' summary.*]

Demonstration of L.E. Cells at Local Inflammatory Sites in Patients with Systemic Lupus Erythematosus. PERILLIE, P. E., CALABRESI, P., and FINCH, S. C. (1960). *New Engl. J. Med.*, **263**, 1052. 4 figs, 14 refs.

In this study of the L.E.-cell phenomenon, reported from Yale Univeristy School of Medicine, New Haven, Connecticut, the authors applied cover-slips to the abraded skin of eleven patients with systemic lupus erythematosus to observe the development of L.E. cells *in situ*. In five of the eleven cases L.E. cells were found adhering to the cover-slips removed 2 to 7 hours after application. Serial examinations showed all stages of L.E.-cell development. The six cases in which a negative result was obtained had received corticosteroid therapy for at least 2 weeks before the test, and it is suggested that the failure to detect L.E. cells in these cases may be due to the decrease in L.E. globulin which is known to occur after such treatment. No L.E. cells were found on cover-slips taken from 36 control subjects who were not suffering from systemic lupus erythematosus. The authors conclude that the cover-slip method is "probably as sensitive as most L.E.-cell tests now in use and may serve as an additional simple diagnostic aid in systemic lupus erythematosus".

M. Wilkinson.

Changes in the Ocular Fundus in Acute Lupus Erythematosus Visceralis. Contribution to the So-called Collagen Diseases. (Über Augenhintergrundsveränderungen beim akuten Lupus erythematodes visceralis. Ein Beitrag zu den sogenannten Kollagenkrankheiten.) JÜTTE, A. (1960). *Klin. Mbl. Augenheilk.*, **137**, 765. 3 figs, 22 refs.

After a brief outline of the general symptoms of lupus erythematosus visceralis and the possible ocular changes associated with it, the frequency of which has been variously estimated as from 25 to 50 per cent., a case history is presented of an 18-year-old girl in whom, during an acute phase of the disease, papilloedema, venostasis, flame-shaped haemorrhages, and cotton-wool exudates in both ocular fundi were seen. After a short treatment with prednisone the general condition improved considerably and the ocular changes disappeared. The ocular pathology is not specific, but the changes would correspond to the increased permeability of the vessels and the blood alterations such as anaemia, dysproteinaemia, and the abnormally increased erythrocyte sedimentation rate which feature prominently in the disease. The very subtle control of the prednisone therapy afforded by ophthalmoscopy proved valuable in this case.

L. Wittels.

Scleromalacia and the Collagen Diseases. (Scléromalacie associée aux collagénoses.) APPELMANS, M., MICHIELS, J., and VERSECKEN, E. (1960). *Bull. Soc. belge Ophtal.*, No. 124, Pt. 2, 912. 2 figs, 41 refs.

Two case reports of women, in whom perforating scleromalacia occurred as a manifestation of lupus erythematosus and nodular periarteritis, showed that all the ocular tissues were involved during the course of the collagen disease. An infectious origin did not seem likely. Neither antibiotics nor corticosteroids could stop the aggravation of the condition which led to blindness.

L. Coppez.

Pathologic Observations concerning the Cutaneous Lesion of Progressive Systemic Sclerosis: an Electron Microscopic Histochemical and Immunohistochemical Study. FISHER, E. R., and RODNAN, G. P. (1960). *Arthr. and Rheum.*, **3**, 536. 6 figs, 14 refs.

This paper from the University of Pittsburgh reports the results of a study of biopsy specimens of skin taken from fifteen cases of progressive systemic sclerosis with varying degrees of scleroderma. Ordinary histological examination in the cases with minimal clinical involvement revealed a variable degree of homogenization of the dermal collagen. In some cases elastic fibres in the upper dermis seemed to be fragmented and increased in number. In the advanced cases all the well-known appearances were found.

Electron microscopy showed no qualitative abnormalities of collagen fibres. Histochemical examination

also revealed no abnormal features; alkaline phosphatase, succinic dehydrogenase, and non-specific esterase were of normal distribution. Staining for polysaccharides gave negative results, as it did in normal skin. Pepsin and collagenase digested the collagen fibres, while deamination and acetylation of sections caused the usual increase in elastic-staining fibres. Oxytalan fibres were present as in normal skin. Staining of fresh frozen sections by fluorescent anti-human γ-globulin, albumin, or fibrinogen showed no abnormalities of localization.

The authors conclude that alterations of dermal collagen in scleroderma are the result of quantitative rather than qualitative changes. *G. Loewi.*

Systemic Lupus Erythematosus. A Review, with a Case of Unusual Longevity. REIFF, S. (1961). *N.Y. St. J. Med.*, **61**, 385. 35 refs.

Systemic Lupus Erythematosus and Normal Antibodies. MUSCHEL, L. H. (1961). *Proc. Soc. exp. Biol. (N.Y.)*, **106**, 622. 14 refs.

Renal Manifestations of Systemic Lupus Erythematosus. A Clinical and Pathological Study of 90 Cases. SOFFER, L. J., SOUTHREN, A. L., WEINER, H. E., and WOLF, R. L. (1961). *Ann. intern. Med.*, **54**, 215. 15 refs.

Avascular (Aseptic) Bone Necrosis associated with Systemic Lupus Erythematosus. DUBOIS, E. L., and COZEN, L. (1960). *J Amer. med. Ass.*, **174**, 966. 4 figs, 10 refs.

Neuritis in Periarteritis Nodosa. (Le neuriti nella periarterite nodosa.) BIGNAMI, A. (1961). *Policlinico, Sez. prat.*, **68**, 577. 16 figs, 44 refs.

Anabolic Hormones in Dermatomyositis. ARMSTRONG, A., and MURDOCH, W. R. (1960). *Brit. med. J.*, **2**, 1929. 2 figs, 11 refs.

Non-Articular Rheumatism

Polymyalgia Rheumatica: a Clinical Study of 21 Cases. GORDON, I. (1960). *Quart. J. Med.*, **29**, 473. 4 figs, 15 refs.

In this report from the Aberdeen Royal Infirmary the author describes a series of 21 patients who had a syndrome consisting of pain and stiffness in the muscles and periarticular tissues in relation to the larger joints of the body. There were eleven women and ten men, and their ages ranged from 49 to 82 years. In twelve in whom the syndrome was fully developed the pain and stiffness were severe enough to immobilize them for a few months. However, joint swelling was observed in only six cases; it was transient and affected fingers and knees. There was no radiological evidence of active arthritis. General symptoms were common, and consisted of loss of weight, anorexia, fatigue, low fever, and insomnia. The erythrocyte sedimentation rate was raised, ranging from 42 to 122 mm. in one hour (Westergren). There was also hypochromic anaemia, with elevation of the plasma globulin. The Rose-Waaler test gave a negative reaction in every case.

In seven cases not treated with steroids the symptoms disappeared completely in 2 to 4 years; in thirteen cases there was a prompt remission after steroid therapy was begun. Relapse occurred in seven cases after the initial course, and two or more courses of steroid therapy were needed.

The author discusses the differential diagnosis from such conditions as cervical spondylosis, secondary carcinoma, myelomatosis, the collagen diseases, and brucellosis. He admits that it may be difficult to distinguish the syndrome from rheumatoid arthritis, but he draws attention to the absence of the arthritis, the absence of joint deformity or ankylosis, and the consistently negative Rose-Waaler reaction. He concludes that polymyalgia rheumatica is a disease *sui generis*, which should be treated, when necessary, by short courses of steroids. *K. C. Robinson.*

General Pathology

Relation between Intravascular Aggregation of the Erythrocytes and the Erythrocyte Sedimentation Rate in the Course of Rheumatic Diseases. (La correlazione tra eritroaggregazione intravascolare e velocità di eritrosedimentazione nel corso di affezioni reumatiche.) PASQUARIELLO, G., and CURTARELLI, G. (1960). *Reumatismo*, **12**, 281. 2 figs, 33 refs.

From observations made by the first-named author on forty patients suffering fron rheumatic diseases and reported previously it was concluded:

(1) That intravascular aggregation of erythrocytes (I.A.E.), visible on biomicroscopy of the conjunctiva, is always to be found in the clinically active stages of rheumatic diseases, even in the absence of symptoms;

(2) That anti-rheumatic treatment (with salicylates or hormones) has no immediate effect on this phenomenon, which persists even after the complete remission of symptoms and disappears only after adequate treatment has been given for several weeks;

(3) That compared with other tests, such as estimation of the blood fibrinogen and mucoprotein concentrations, the biomicroscopical test appears to provide the most reliable means of assessing rheumatic activity, particularly during treatment with corticosteroids.

The present paper reports the results of a study of the relationship between I.A.E. and the erythrocyte sedimentation rate (E.S.R.) on forty patients suffering from rheumatic diseases (fourteen with acute articular rheumatism, six with active rheumatic carditis, fourteen with rheumatoid arthritis, and six with "subevolutive rheumatism"). All these patients were treated with salicylates (aspirin 3 to 4 g. or sodium salicylate 2 to 4 g. daily), corticosteroids (prednisone 20 to 40 mg. or dexamethasone 15 to 30 mg. daily), or both, usually for 2 to 3 months. The E.S.R. was measured and the degree of

I.A.E. assessed according to a defined scale at frequent intervals throughout the course of treatment.

It was found that the I.A.E. values were constantly increased in active rheumatic conditions and frequently remained high for some time after the E.S.R. had fallen to normal levels as a result of treatment. It is pointed out that I.A.E. is determined not only by haematological changes, but also by systemic changes in the capillary circulation, and it is suggested that this may account for the lack of correlation with the E.S.R. during the phase of apparent clinical remission. From their findings the authors reach the following conclusions:

(1) Although not specific, the assessment of I.A.E. may be considered to be among the most useful tests for the diagnosis of rheumatic conditions, giving a true picture of the degree of activity of the disease, which is modified only slowly and temporarily by therapy;
(2) When the E.S.R. is definitely raised the I.A.E., which is invariably increased in such cases, does not provide any additional help in diagnosis or prognosis.
(3) On the other hand, when the E.S.R. is normal or nearly normal, especially after protracted treatment, the finding of a clearly positive I.A.E. value may be useful in indicating the presence of rheumatic activity and giving warning of the probability of a recurrence, enabling the appropriate therapy to be given without delay.

R. E. Lister.

Studies of Chronic Rheumatic Polyarthritis with Negative Rose-Waaler Reaction. (Études sur les polyarthrites chroniques rhumatismales avec réaction de Waaler-Rose négative.) DE SÈZE, S., RYCKEWAERT, A., KAHN, M. F., BADIN, J., and DEBEYRE, N. (1960). *Rev. franç. Ét. clin. biol.*, **5**, 901. 33 refs.

In the study here reported from the Hôpital Lariboisière, Paris, a group of 33 patients with rheumatoid arthritis satisfying the criteria of the American Rheumatism Association (A.R.A.) who showed a negative result in the differential agglutination test (D.A.T.) was compared with another group of seventy D.A.T.-positive cases in order to ascertain if the D.A.T.-negative group contained patients with diseases other than rheumatoid arthritis. [In making this comparison the authors do not state how the cases were selected and whether any attempt was made to match the groups for such factors as age and duration of disease.]

The results were as follows, figures in parentheses referring to the D.A.T.-positive group:

(1) Proportion conforming to A.R.A. criteria for "definite" and "classic" rheumatoid arthritis 57 per cent. (88·5 per cent.);
(2) assessed as mild cases (Steinbrocker classification I), 61 per cent. (23 per cent.);
(3) Radiographic erosions present 42·5 per cent. (84 per cent.);
(4) Subcutaneous nodules present 6 per cent. (84 per cent.);
(5) Male patients 12 per cent. (31 per cent.);
(6) Rapid onset of the disease 18 per cent. (31 per cent.);
(7) Elevated erythrocyte sedimentation rate (over 50 mm. in one hour at some time in the disease) 18 per cent. (43 per cent.);
(8) L.E. cells found 3 per cent. (4 per cent.);
(9) Lymphadenopathy present 9 per cent. (60 per cent.);
(10) Typical clinical picture 33 per cent. (70 per cent.).

[The authors define the typical clinical picture as: duration of one year or more, swelling of at least one joint, involvement of at least four joints, localization in the wrists, metacarpo-phalangeal or elbow joints, radiological erosions of subarticular bone, ulnar deviation of fingers, flexion deformities of metacarpo-phalangeal or proximal interphalangeal joints, and marked stiffness of at least one joint other than the shoulder.]

Among the D.A.T.-negative cases were found one which might have been *pseudopolyarthrite rhizomélique* of Forestier and Certociny, two resembling infective arthritis with persistent residua, five with mild disease, that is, an arthralgia rather than an arthritis (four of the D.A.T.-positive cases were of this nature), and eight with osteo-arthrosis with signs of an inflammatory process as well (usually seen in elderly women).

The authors summarize their results in the following generalizations: D.A.T.-negative rheumatoid arthritis differs from D.A.T.-positive disease in that it less often affects men, less frequently starts suddenly, less often presents the typical clinical picture, is accompanied by less deformity of the hands, shows radiologically fewer erosions of bone, less stiffness, less adenopathy, and fewer signs of inflammation. *Allan St. J. Dixon.*

Technical Errors in the Blood Sedimentation Rate Estimation. LEWSEY, D. M., and SIMPSON, J. M. (1960). *Guy's Hosp. Rep.*, **109**, 160. 4 figs, 7 refs.

An investigation was carried out at Guy's Hospital, London, to assess the extent to which errors arose in the estimation of erythrocyte sedimentation rates. Such estimations are made as a routine by Westergren's method on the medical wards. The most important cause of error was the fact that the tubes were often not properly vertical because the stands were warped; errors of up to 300 per cent. could occur in this way. Other important sources of error were inaccurate measuring of citrate dilutions and failure to dry the tubes properly before filling. Variations in ward temperature and draughts were found not to be very important. A technique designed to eliminate such errors is described.

M. C. G. Israels.

Levels of the Protein Fractions and Cholinesterase in the Serum as Indices of the Activity of the Rheumatic Process in Children. [In Russian.] OKULOVA, E. M. (1960). *Sovetsk. Med.*, **25**, 9. 16 refs.

The serum protein fractions were analysed by means of paper electrophoresis in eleven healthy control subjects

and 131 patients with acute rheumatism, the manifestations of which were cardio-articular in 38 cases, cardiac in 22, neurological in 34, and latent in 37. In all forms of the disease there was a considerable change in the protein fractions, but little change in the serum total protein values. The albumin level was low in patients with active disease, the extent of the fall in this level being directly proportional to the severity of the disease; thus the lowest values (22 to 24 per cent. of the total serum protein) were observed during the acute stage of the cardio-articular form of the disease, while the least fall (31 to 35 per cent. of total protein) was noted in patients with chorea and latent rheumatism. Recovery was associated with return of the serum albumin level to normal. The hypoalbuminaemia was associated in the acute stages with a rise in level of the α-globulin, particularly of the α_2-fraction (maximum increase 24 to 34 per cent.). In the majority of patients with latent rheumatism the α-globulin fraction reached a value of 7 to 10 per cent. of the total serum protein value; in some of these patients the α_2-globulin fraction was also high, but this occurred only in the presence of definite cardiac or tonsillar involvement. With clinical recovery, the α_2-fraction returned rapidly and the α_1-fraction less uniformly to normal, only to rise again during exacerbations. The level of the β-globulin fraction was also usually high, particularly in acute stages of the cardiac form of the disease, but also in latent rheumatism. The γ-globulin fraction rose rather late in the acute or subacute stage, but remained normal in the latent stage. In all cases the dysproteinaemia was accentuated by an intercurrent disease. Examination of the serum and defibrinated contents of cantharidin-induced blisters revealed similar changes in the protein pattern.

Serum cholinesterase activity was then determined by the Pravdich-Neminskaya technique in 68 patients and eight control subjects aged 4 to 15 years. In the controls this value ranged from 47·32 to 58·25 per cent. In all patients in the acute stage of the disease the serum cholinesterase activity was reduced, falling to 20 per cent. in patients with disturbed cardiac action. Even steady clinical recovery was associated with oscillations in the serum cholinesterase level, probably reflecting the variations in tonus of the vegetative nervous system. No definite correlation could be demonstrated between the changes in the serum protein fractions and those in serum cholinesterase activity. However, the author concludes that a low amplitude of oscillation of serum cholinesterase activity combined with a considerable degree of dysproteinaemia is of bad prognostic significance, even in patients who appear to be improving clinically. *S. W. Waydenfeld.*

***In vitro* Investigations of Two Types of Lupus Erythematosus Plasma Factor.** BENCZE, G., and LAKATOS, L. (1960). *Brit. med. J.*, **2**, 1571. 5 refs.

Previous studies at the University Medical School, Szeged, Hungary, have shown that the L.E. factor from some, but not all, patients with systemic lupus erythematosus (S.L.E.) can be transferred to human beings or animals by plasma transfusion. The present experiments further distinguish the transferable from the non-transferable type of L.E. factor.

Plasma from eight cases of S.L.E. proved non-transferable, and these plasma specimens produced abundant L.E. cells when mixed with the corresponding patient's leucocytes, but few or no L.E. cells when added to leucocytes from healthy subjects. On the other hand five S.L.E. patients donated plasma containing transferable L.E. factor, and these specimens produced many L.E. cells with leucocytes from the patients as well as with leucocytes from healthy donors.

[The quantitation of L.E.-cell tests is unsatisfactory and provides only suggestive evidence.] *M. Wilkinson.*

Antinuclear Factors in the Serum of Relatives of Patients with Systemic Lupus Erythematosus. POLLAK, V. E., MANDEMA, E., and KARK, R. M. (1960). *Lancet*, **2**, 1061. 2 figs, 13 refs.

In view of recent reports of the familial occurrence of systemic lupus erythematosus (S.L.E.) the authors examined sera from relatives of patients with this disease for the presence of antinuclear antibodies, using the fluorescein-labelled antibody technique.

When the serum dilution was 1 : 4 or higher, positive results were obtained initially with serum from 45 out of 51 patients with S.L.E. At these dilutions sera from forty healthy subjects were negative. The result of the test was therefore regarded as positive when antinuclear factors could be demonstrated in serum diluted 1 : 4 or more. On this basis positive results were obtained with 24 simple samples of serum from fifty relatives of twelve patients with S.L.E. The incidence of positive results was particularly high in female relatives (seventeen out of 26).

The gamma-globulin levels of the sera of these fifty relatives were estimated by the biuret method and paper electrophoresis. Levels above the normal range (+2 S.D. of the mean for 62 healthy controls) were found in only 5 and levels below that range in three.

M. Wilkinson.

Relations between the Antinuclear, Rheumatoid, and L.E.-Cell Factors in the Systemic Rheumatic Diseases. HALL, A. P., BARDAWIL, W. A., BAYLES, T. B., MEDNIS, A. D., and GALINS, N. (1960). *New Engl. J. Med.*, **263**, 769. 29 refs.

The authors, working at the Robert Breck and Peter Bent Brigham Hospitals, Boston, have performed the latex-fixation test with the euglobulin and inhibition modifications, the L.E.-cell test, and the fluorescent antibody test for anti-nuclear globulin on the sera of 130 patients with definite or classic rheumatoid arthritis, 22 with clinically typical systemic lupus erythematosus and a positive response to the L.E.-cell test, seventeen with scleroderma, polyarteritis, or dermatomyositis, and 100 patients who served as controls, some of whom had

discoid lupus, psoriasis, other skin diseases, or hepatic disease.

All the patients with systemic lupus erythematosus showed a positive result in the anti-nuclear factor test. The latex-fixation test on the serum was negative in all cases, was positive on the euglobulin fraction in two cases, and positive in the inhibition test in an additional four cases. Of the 130 patients with rheumatoid arthritis 122 gave a positive latex-fixation reaction on the serum, seventeen patients (13 per cent.) consistently showing positive L.E.-cell tests, and 36 per cent. positive anti-nuclear factor tests, while seven patients had a positive result in the L.E.-cell test and a negative result in the anti-nuclear factor test. However, on testing the euglobulin fraction of fifteen patients with negative serum anti-nuclear factor tests eleven (73 per cent.) were positive. Likewise, two out of fourteen patients with positive anti-nuclear factor and a negative L.E.-cell preparation gave positive L.E.-cell tests on the euglobulin fraction. Thus over 80 per cent. of patients with clinical rheumatoid arthritis had nuclear binding factor. The L.E.-cell preparation and anti-nuclear factor tests were more often positive in patients with severe disease and considered joint destruction.

Of ten patients with scleroderma eight gave positive anti-nuclear factor tests and the remaining two showed a positive result with the euglobulin fraction. Latex-fixation tests were positive in four cases (in the euglobulin test in one and in the inhibition test in three, while two patients had positive L.E.-cell tests. One out of four patients with polyarteritis and two out of three with dermatomyositis gave positive results in the anti-nuclear factor tests. One patient with arthritis due to rubella had a positive L.E. test and antibody test result during the active phase of the disease. A few patients with unclassified musculo-skeletal complaints had positive anti-nuclear factor tests. One patient with reflex sympathetic dystrophy, one with regional enteritis and arthritis, and one with Reiter's syndrome also gave a positive reaction.

Absorption with histone caused the anti-nuclear factor and L.E.-cell activity to disappear in parallel, while the rheumatoid factor and blood group antibody titres were unchanged. The precipitate produced L.E.-cells, while material eluted from the precipitate showed anti-nuclear factor activity. The rheumatoid factor could be selectively absorbed by bentonite coated with pooled human Fraction 2 (gamma globulin). The results showed that anti-nuclear factor and L.E. factor occurred in rheumatoid arthritis as well as in systemic lupus erythematosus. The authors conclude that the frequency with which the factors occurred in these different diseases renders the interpretation of their pathogenetic significance difficult and limits the use of the serological findings in defining separate syndromes. *G. L. Asherson.*

Rheuma-Test in Aetiological Research in Uveitis. (Il reuma-test nell'indagine eziologica delle uveiti.) BUCCI, M. G. (1960). *Boll. Oculist.*, **39**, 501. 33 refs.

The reaction of the polystyrene "latex-fixation" (rheuma-test) is positive in the diagnosis of rheumatic diseases. It was studied in 150 eyes with uveal inflammations of unknown aetiology and was positive in 139 cases. *G. Cristini.*

Immunological Problems concerning Focal Infection and Rheumatism. (Immunologische Probleme beim Fokalinfekt und Rheumatismus.) DITTMAR, F. (1961). *Med. Welt*, No. 18, p. 951. 22 refs.

Physiologic Disposition and Uricosuric Effect of a Keto Analogue of Oxyphenbutazone (G.29701). SEEGMILLER, J. E., DAYTON, P. G., and BURNS, J. J. (1960). *Arthr. and Rheum.*, **3**, 475. 5 figs, 15 refs.

Mechanism of Particulate Carrier Reactions. I. Adsorption of Human γ-Globulin to Polystyrene Latex Particles. ORESKES, I., and SINGER, J. M. (1961). *J. Immunol.*, **86**, 338. 2 figs, 22 refs.

II. Sensitizing Capacity of Various Human Gamma Globulins for Latex Particles. SINGER, J. M., ALTMANN, G., GOLDENBERG, A., and PLOTZ, C. M. (1960). *Arthr. and Rheum.*, **3**, 515. 11 refs.

Entrance of Glucose and Other Sugars into Joints. ROPES, M. W., MULLER, A. F., and BAUER, W. (1960). *Arthr. and Rheum.*, **3**, 496. 11 figs, 36 refs.

Studies of Arthritis and Other Lesions induced in Rats by Injection of Mycobacterial Adjuvant. V. Changes affecting the Skin and Mucous Membranes. PEARSON, C. M., WAKSMAN, B. H., and SHARP, J. T. (1961). *J. exp. Med.*, **113**, 485. 11 figs, 74 refs.

ACTH, Cortisone, and Other Steroids

Comparison of the Growth Suppressive Effect of Cortisone, Prednisone, and Other Adrenal Cortical Hormones. VAN METRE, T. E., JR., NIERMANN, W. A., and ROSEN, L. J. (1960). *J. Allergy*, **31**, 531. 5 figs, 19 refs.

A study was carried out at the Johns Hopkins Hospital, Baltimore, Maryland, to compare the growth-inhibiting effects of prolonged treatment with corticosteroids in children with intractable bronchial asthma. In most of the nineteen cases studied the asthma had started in the first 2 years of life; treatment was with maintenance doses of various corticosteroid preparations. In every case the steroid drug was frequently changed and there were intervals when none was given. Linear growth and weight gain were plotted against the normal development. It was found that cortisone did not impair normal linear growth, whereas most of the other steroids did. [The accompanying table shows that linear growth was completely suppressed in only six instances, in five of which the corticosteroid was given for periods as short as one to 4 months; there are eleven other examples in which less than 50 per cent. of normal linear growth occurred, but here also the period of observation was often not long enough to exclude a natural temporary interruption of linear growth, as is often seen in children.

The cortisone- and corticosteroid-free periods, however, are much longer, and therefore do not contain this element or error. The evidence for the growth-suppressive effect of prednisone and other corticosteroid preparations will, in the circumstances, require strengthening.] *H. Herxheimer.*

Cortisone in the Treatment of Severe Pneumonia in Children during the First Year of Life. [In Russian.] PATUŠINSKAJA, R. A., and STROEVA, E. V. (1960). *Pediatrija*, **38**, 49. 10 refs.

Dyspnoea is usually the first symptom of pneumonia. The younger the child, the earlier appears the condition of respiratory-circulatory insufficiency and so more quickly may the child succumb. Antibiotics alone cannot help the child out of this respiratory dilemma. In such cases the authors recommend the use of cortisone, which has an anti-shock, anti-histamine, and anti-inflammatory action and also increases the antitoxic function of the liver.

In the present study cortisone was given to 31 children with pneumonia, in addition to the usual supportive therapy, which included good nursing, adequate feeding, abundance of vitamins, especially vitamin D, oxygen therapy when required, a combination of two antibiotics, and cardiac stimulants if necessary. The initial dosage of cortisone was 5 mg. per kg. body weight given intramuscularly in three or four doses, this dose being reduced every 2 days during the period of administration, which lasted from 5 to 8 days. The total dose of cortisone, which varied according to the weight of the patient and the severity of the condition, ranged from 50 to 160 mg. In 22 cases, cortisone was administered right from the start. In all cases amelioration of the respiratory and circulatory symptoms was observed within 12 to 24 hours (in a few cases within a few hours) and none of these patients died. In the control group, which consisted of eighteen children who were not given cortisone, five died. *H. W. Swann.*

Triamcinolone in the Treatment of Diseases affecting Collagenous Tissues. [In Russian.] ASTAPENKO, M. G., and NASONOVA, V. A. (1960). *Sovetsk. Med.*, **12**, 42. 2 figs, 9 refs.

Triamcinolone (hydroxyprednisolone) is a very active glucosteroid having greater anti-inflammatory properties than cortisone and its derivatives, while its effect is 1½ times that of prednisone. It does not cause sodium retention or increased potassium loss, nor does it increase arterial tension or lead to osteoporosis. Above all, it does not depress adrenal function.

In this paper the authors report the results in twenty patients with rheumatoid arthritis and ten with other collagenous diseases (seven with systemic lupus erythematosus and three with systemic scleroderma) who were treated with triamcinolone in a dosage of 8 to 16 mg. daily initially, the dose being gradually reduced over the course which lasted 30 to 45 days. All but four of the twenty rheumatoid arthritic patients had previously undergone prolonged but ineffective treatment with prednisolone. In addition to triamcinolone, ten received "crysanol", nine pyrazolone preparations, and one resochin. The response to treatment was rapid, being evident in six cases within 24 hours; on the other hand four patients showed no marked improvement after 4 weeks' treatment. Of the thirty patients, twelve became afebrile, and in eleven the erythrocyte sedimentation rate fell to normal and remained so. At the end of the course, six of the rheumatoid patients were much improved (loss of pain, subsidence of joint exudates, and increased range of movement)—this group including four of those who had not benefited from prednisolone—eight were improved, four slightly improved, and two were not improved. Of these last, one had visceral amyloidosis and the other a very active form of arthritis, with contractures, ankylosis, and psoriasis. In the other ten patients there was considerable symptomatic relief, but the pathology remained unchanged. One patient with scleroderma died of renal failure, and three of those with lupus erythematosus succumbed to infections. The authors conclude that triamcinolone is less prone to cause side-effects than other steroids, and is specially indicated in patients with obesity, arterial hypertension, or oedema. *L. Firman-Edwards.*

Interstitial Plasma-cell Pneumonia after Treatment with Corticosteroids. (Interstitielle plasmacelluläre Pneumonie nach Corticosteroidbehandlung.) MÜLLER, G. (1960) *Frankfurt. Z. Path.*, **70**, 657. 9 figs, bibl.

The histology of the lungs was examined at the Pathological Institute of the University of Tübingen in seven children who had died of interstitial plasma-cell pneumonia after about 2 months' continuous corticosteroid therapy. At death the children were aged 8 months to 12 years. In all cases *Pneumocystis carinii* was seen in the sections, but otherwise the histological picture differed from that of untreated cases. The main difference was in the presence in the interstitial tissue of reticulo-histiocytic proliferation and a paucity of lymphocytes, whereas plasma cells and lymphocytes are prominent in untreated cases. However, there was a relative increase in the number of plasma cells in the alveolar septa.

The histological appearances in the treated cases were essentially the same at all ages. The severity of the disease was unchanged. *M. Lubran.*

Methylprednisolone Acetate: A Single Preparation Suitable for Both Intra-Articular and Systemic Use. NORCROSS, B. M., and WINTER, J. A. (1961). *N.Y. St. J. Med.*, **61**, 552. 1 fig., 25 refs.

Observations on the Management of Rheumatoid Arthritis and Related Disorders with the Newer Corticosteroids. ROBINS, H. M. (1961). *N.Y. St. J. Med.*, **61**, 717. 14 refs.

Danger of Corticotropin in Addison's Disease. STONE, D. B., and JEWEL, J. G. (1961). *Arch. intern. Med.*, **107**, 372. 13 refs.

Digestive Complications of Adrenal Corticotherapy in Rheumatology. (Accidents digestifs de la corticothérapie surrénale en rhumatologie.) LAYANI, F., WATTEBLED, R., and PEYRON, J. (1961). *Sem. Hôp. Paris*, **37**, 1047. 103 refs.

Gastro-intestinal Side-effects of Corticosteroid Therapy. (Accidents digestifs de la corticothérapie.) SERRE, H., and SIMON, L. (1960). *Rev. Rhum.*, **27**, 523; *Rhumatologie*, **12**, 229.

Secondary Effects of Corticosteroid Treatment. (Sur les effets secondaires des traitements corticostéroidiens.) JUNET, R. (1961). *Rev. méd. Suisse rom.*, **81**, 246.

Epileptic and Psychiatric Side-effects of Corticotherapy. (Accidents épileptiques et troubles psychiques des traitements cortico-surrénaliens.) LAURAS, A. (1960). *Rev. Rhum.*, **27**, 524; *Rhumatologie*, **12**, 258.

Examples of Good Tolerance of Corticosteroids. (Exemples de bonne tolérance des corticostéroïdes.) THÉVENOZ, F. (1961). *Rev. méd. Suisse rom.*, **81**, 241.

Neuro-psychiatry and Steroid Therapy. Neurological Side-effects. (Neuro-psychiatrie et corticothérapie. Les accidents neurologiques.) FAULONG, L., and LAURAS, A. (1960). *Rhumatologie*, **12**, 250.

Some Rare Side-Effects of Steroid Therapy for Rheumatic Diseases. (Sur quelques rares effets collatéraux en cours de thérapie stéroïdienne des maladies rhumatismales.) SCALABRINO, R. (1960). *J. belge Méd. phys. Rhum.*, **15**, 206. 13 figs, 30 refs.

Systemic Manifestations of Rheumatoid Arthritis (Rheumatoid Disease) accentuated by Steroid Therapy. PAUL, W. D. (1961). *J. Iowa St. med. Soc.*, **51**, 205. 111 refs.

Other General Subjects

Clinical Investigation of a New Antirheumatic Combination of Pyrazolone and Pyrazolidine Derivatives. (Sperimentazione clinica di un nuovo anti-reumatico pirazolon-pirazolidinico.) CIOCCI, A. (1960). *Minerva med.* (*Torino*), **51**, 3496.

The author of this paper from the Institute of Rheumatology of the University of Rome describes the results obtained in treating 91 patients with "tomanol", a new preparation consisting of two parts of "isopyrin" (1-phenyl-2:3-dimethyl-4-*iso*propylamino-5-pyrazolone) combined with one part of phenylbutazone (sodium salt). There were six cases of rheumatic fever, eight of rheumatoid arthritis, seven of "secondary rheumatism", 38 of osteo-arthritis (primary and secondary), ten of intervertebral disk syndrome, fourteen of "arthromyalgic syndromes" of varying aetiology, three of trigeminal neuralgia, and five of pain due to metastatic tumours.

After routine physical, radiological, and laboratory examination followed by a control period of rest in bed for 5 to 7 days, treatment was started with 2 to 4 tablets, 2 suppositories, or 1 to 2 ampoules of tomanol daily [exact dosage not stated] with meals, the dose being increased or diminished subsequently according to effect and tolerance. No other drugs were given, and treatment was continued for at least 3 weeks.

The results of treatment, as judged from the effect on the clinical and humoral signs of rheumatic activity, were "excellent" in 48 cases (53 per cent.), "good" in 21 (24 per cent.), "fair" in eight (8 per cent.), and "inadequate" in fourteen (15 per cent.). On the basis of these findings the author considers that tomanol deserves to be added to the list of active anti-rheumatic drugs. This favourable opinion was confirmed by an additional test on ten of the patients who had given an excellent or good response to tomanol, but relapsed within one to 4 days when a placebo was substituted. In some cases an ephemeral increase in severity of symptoms was observed after the start of treatment, but this did not prevent a subsequent excellent response. Only sixteen patients could be kept under observation, of whom ten were free of symptoms 40 days after the conclusion of treatment. *Robert E. Lister.*

Rare and Little-Known Sites of Articular and Non-articular Rheumatic Conditions. (Localizaciones raras y poco conocidas de los procesos reumáticos articulares y abarticulares.) COSTA BERTANI, G. (1960). *Rev. argent. Reum.*, **25**, 284. 45 refs.

Continuous Association of Poverty with Intensity of Rheumatic Manifestations. COBURN, A. F. (1960). *Amer. J. med. Sci.*, **240**, 687. 5 figs, 36 refs.

Rheumatism and Arthritis: Review of American and English Literature of Recent Years (Thirteenth Rheumatism Review) (1960). *Ann. intern. Med.*, **53**, No. 7, p. 2. 3,430 refs.

Congenital Rigidity of the Joints. (Le rigidità congenite articolari.) PISCONTI, G., and GIORDANO, S. A. (1961). *Minerva pediat.* (*Torino*), **13**, 442. 9 figs, 80 refs.

The Painful Shoulder and the Blocked Shoulder. An Anatomical and Arthrographic Study. (L'épaule douleureuse et l'epaule bloquée. Une étude anatomique et arthrographique.) SÈZE, S. DE, HUBAULT, J., CAROIT, M., POINSARD, G., RENIER, J.-CL., RYCKEWAERT, A., and WELFLING, J. (1961). *Un. méd. Can.*, **90**, 351.

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